Médecine préventive et génétique: de la recherche à la pratique
Clinique: Exemple de la Néphrogénomique@Sorbonne Université

Pr. Laurent MESNARD

Centre de Référence Marhea (Filière maladie rare ORKID)

Centre national de référence – CNR-MAT (Filière maladie rare MARIH)

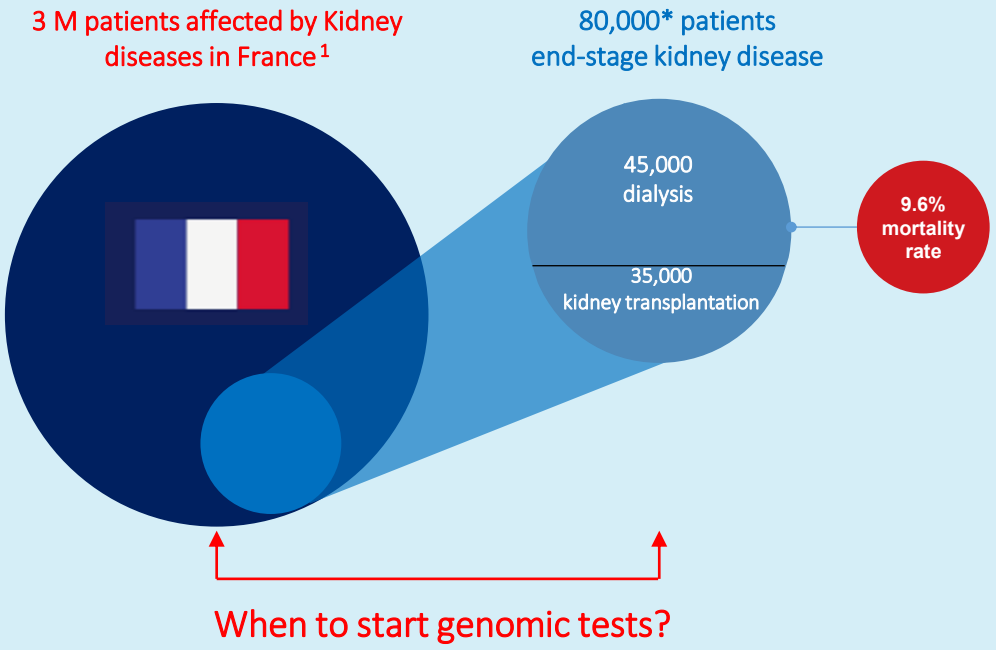
APHP. Sorbonne Université

INSERM UMR115, Hôpital Tenon

PARIS

https://www.nephrogenomics.com

Adult's Chronic kidney diseases: genomic analysis could impact up to 30% of diagnoses[1]



Among them:

- 19–30% familial history of ESKD
- 12% autosomal dominant polycystic kidney disease
- **20–30% unknown nephropathy**
- **10–40% are of genetic origin**

Risk stratification for non-mendelian diseases:

- APOL1
- Low penetrance variants (CFH, CFI, CD46…)
- Polygenetic risk scores (PRS)
- **Kidney transplantation**

*Excluded: patients with genetic disease that does not lead to ESKD.
CKD, chronic kidney disease; ESKD, end-stage Kidney disease; M, million.

1. Agence de la biomédecine. Rapport Annuel 2016. Available at https://www.agence-biomedecine.fr/IMG/pdf/rapportrein2016.pdf. Accessed April 2022.

Prevalence of unknown nephropathies (CKDx) in the French REIN registry 2019[1]

A definition of unknown nephropathies ?

Clinical vignette 1

- 33-year-old patients with malignant hypertension, KDIGO3 acute renal failure, vascular lesion on renal biopsy

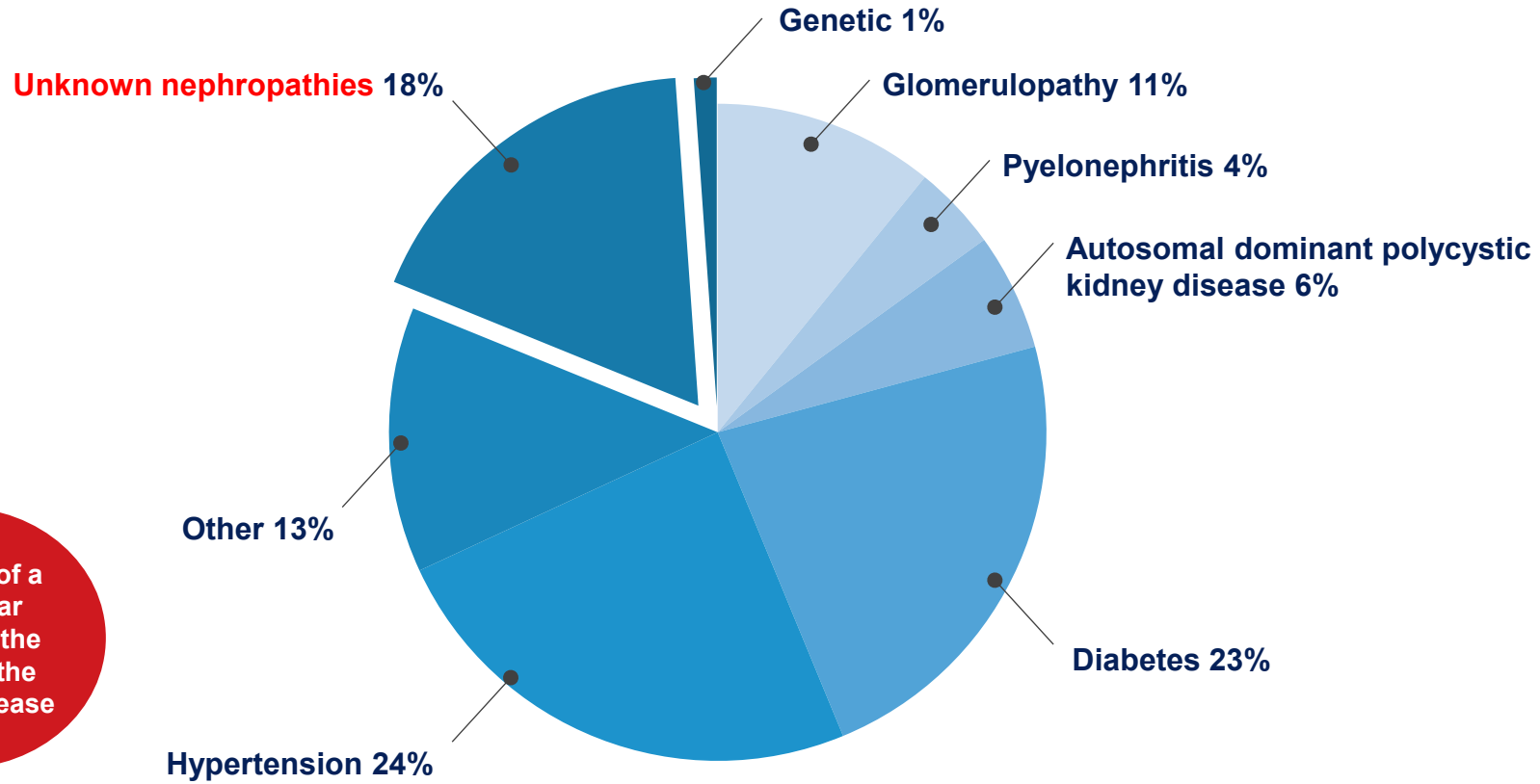
Clinical vignette 2

- 24-year-old patient with severe hypertension
- TMA on renal biopsy

Clinical vignette 3

- 43-year-old patient with severe hypertension and hematuria
- FSGS on renal biopsy

Absence of a molecular trigger at the origin of the kidney disease

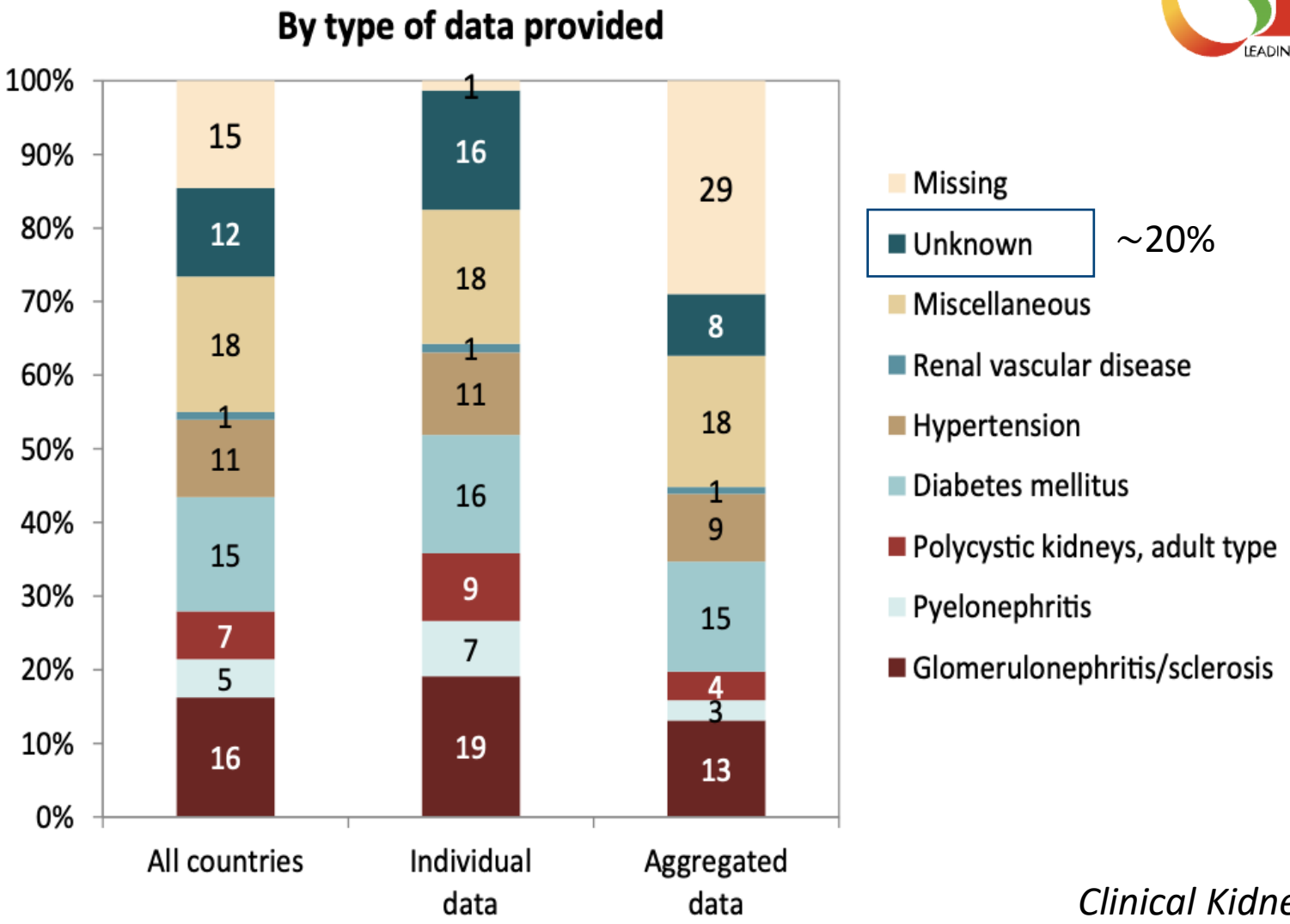


REIN, Réseau Epidémiologique et Information en Néphrologie.

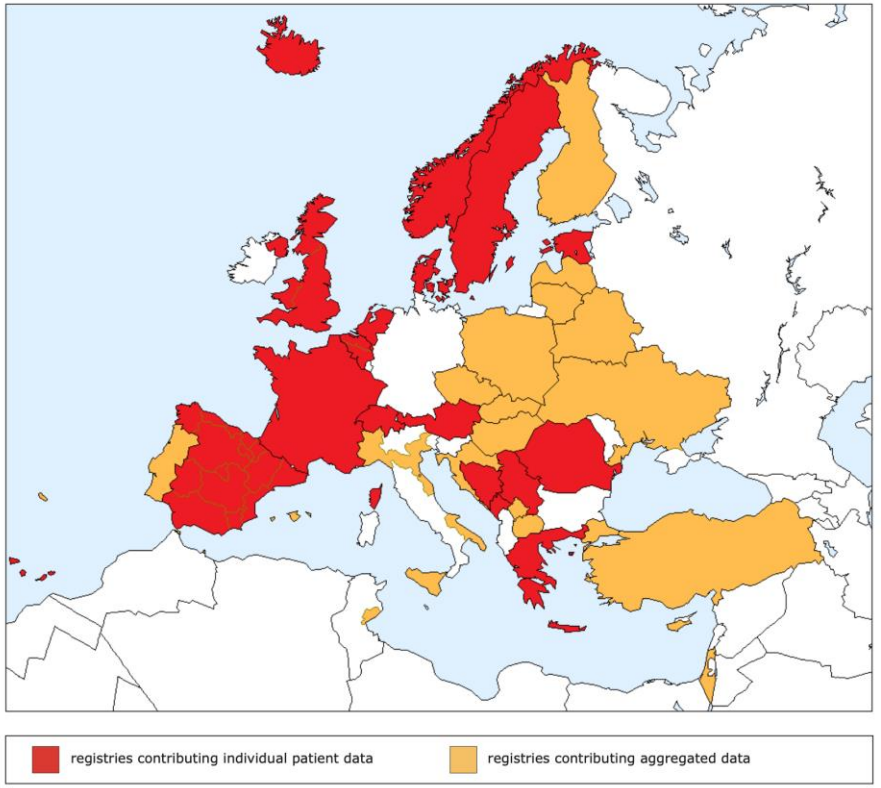
1. Agence de Biomédecine. Rapport Annuel 2019. Available at https://rams.agence-biomedecine.fr/. Accessed April 2022.

Prevalence of unknown nephropathies (CKDx) in Europe

ERA Registry Annual Report 2022



~20%



Clinical Kidney Journal, Volume 18, Issue 2, February 2025

Unknown nephropathies (CKDx) are often caused by monogenic disorders, Groopman et al. 2019

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Diagnostic Yield and Heterogeneity of Genetic Diagnoses across Clinical Diagnostic Categories.

Clinical Diagnosis	Sequencing Performed	Diagnostic Variants Present	Diagnostic Yield	Distinct Monogenic Disorders Detected	Singleton Genetic Diagnoses
	number of patients		*percent*	*number*	
Congenital or cystic renal disease	531	127	23.9	27	20
Glomerulopathy	1411	101	7.2	23	14
Diabetic nephropathy	370	6	1.6	3	2
Hypertensive nephropathy	319	8	2.5	6	4
Tubulointerstitial disease	244	11	4.5	10	9
Other	159	6	3.8	4	2
Nephropathy of unknown origin	281	48	17.1	28	17
Total	3315	307	9.3	66*	39*

ORIGINAL ARTICLE

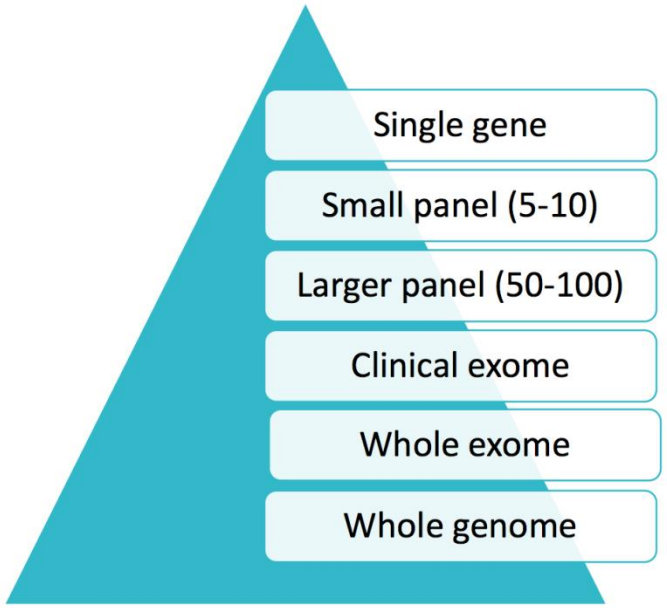
Diagnostic Utility of Exome Sequencing for Kidney Disease

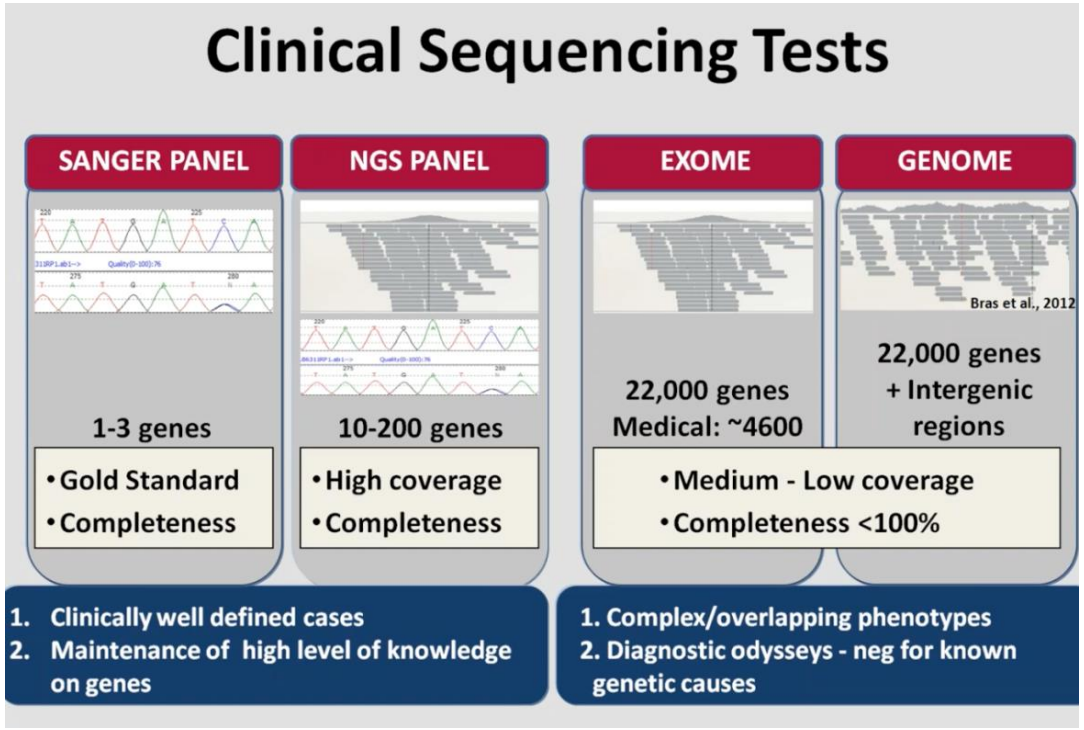
More than 3000 unselected CKDs, US patients

- 90% adults
- 55% of European ancestry
- **17% diagnostic yield for unknown nephropathies**
- 66 different monogenic disorders

N Engl J Med 2019;380:142-51

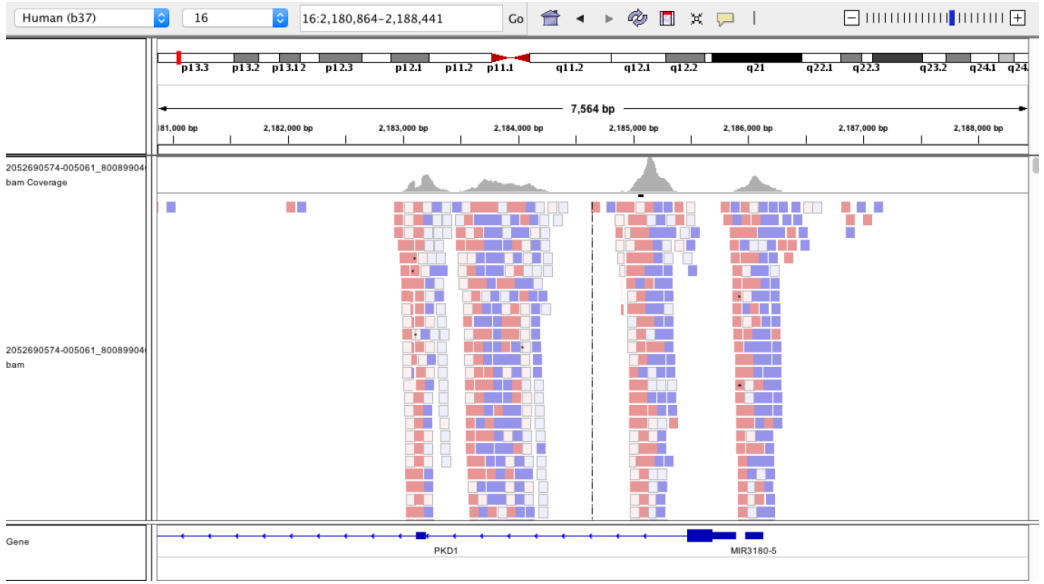
The evolution of sequencing since 2011





Current genetic testing tools and methods for standard care

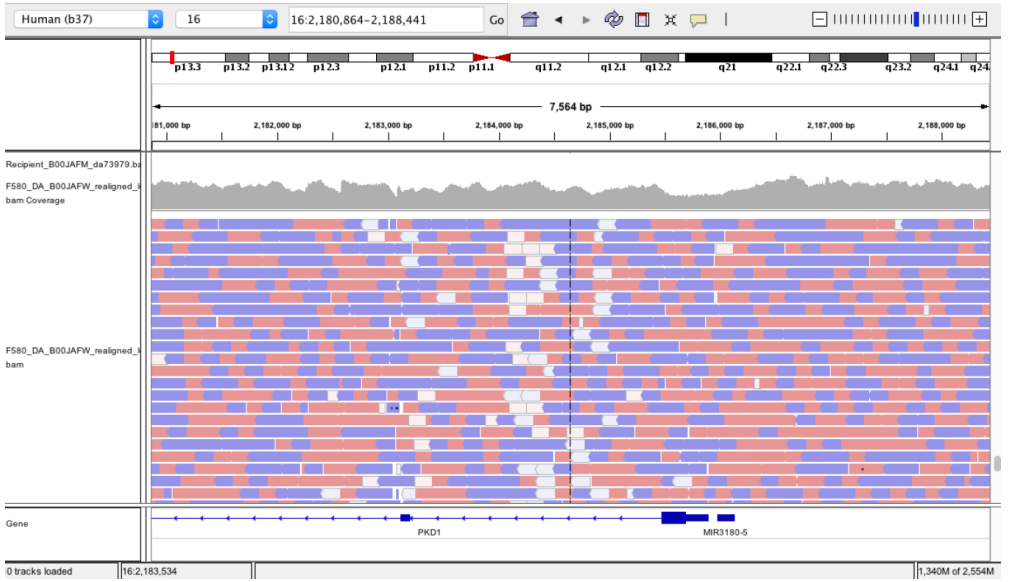
Whole exome sequencing (WES) or Gene Panels



Exome/panel

- Exome = 5% of genome
- 21,000 genes (“Mendeliome” – 4,000 genes)
- Bioinformatics/In silico panels (818 genes for kidney diseases at SU)

Whole genome sequencing (WGS)



WES, whole exome sequencing; WGS, whole genome sequencing.

Whole exome sequencing (WES) workflow at Sorbonne Université

Example

Cystic nephropathy of unknown origin

Nephrogenomic consultation

- Phenotyping, family history
- Information and consent

(WES/WGS)

Sequencing and analysis

4 to 6 weeks

File

Molecular diagnosis

Second consultation

Retrophenotyping

Genetic counseling

Le Réseau Néphrogénomique Sorbonne Université en 2026

Le centre de APHP.Sorbonne Université est devenu un Pôle de référence en ile de France.

https://www.nephrogenomics.com

Staff Interne

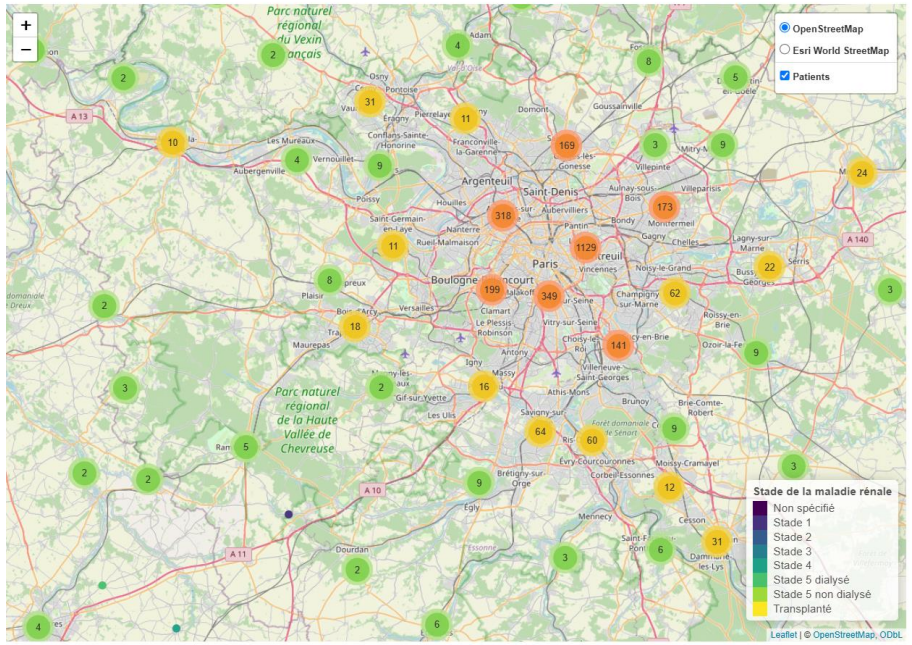
35 prescripteurs formés en 2025 (vs 12 en 2021) (au moins une prescription)

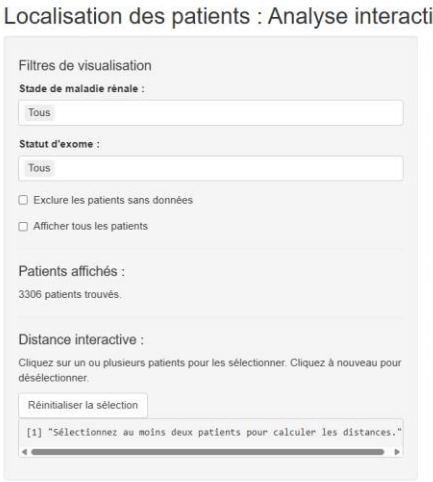
Réseau Externe

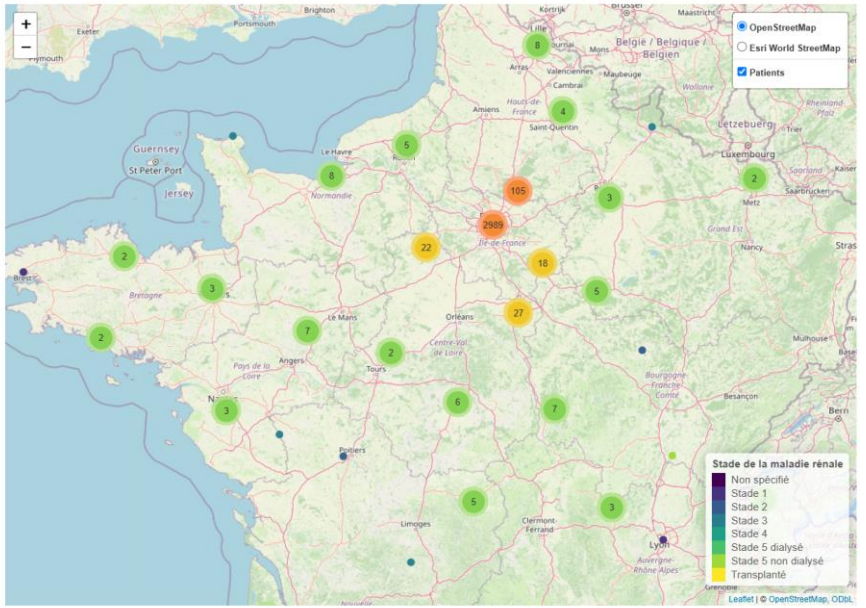
142 médecins adresseurs uniques, en 2025 (x3.1 depuis 2021).

Origine

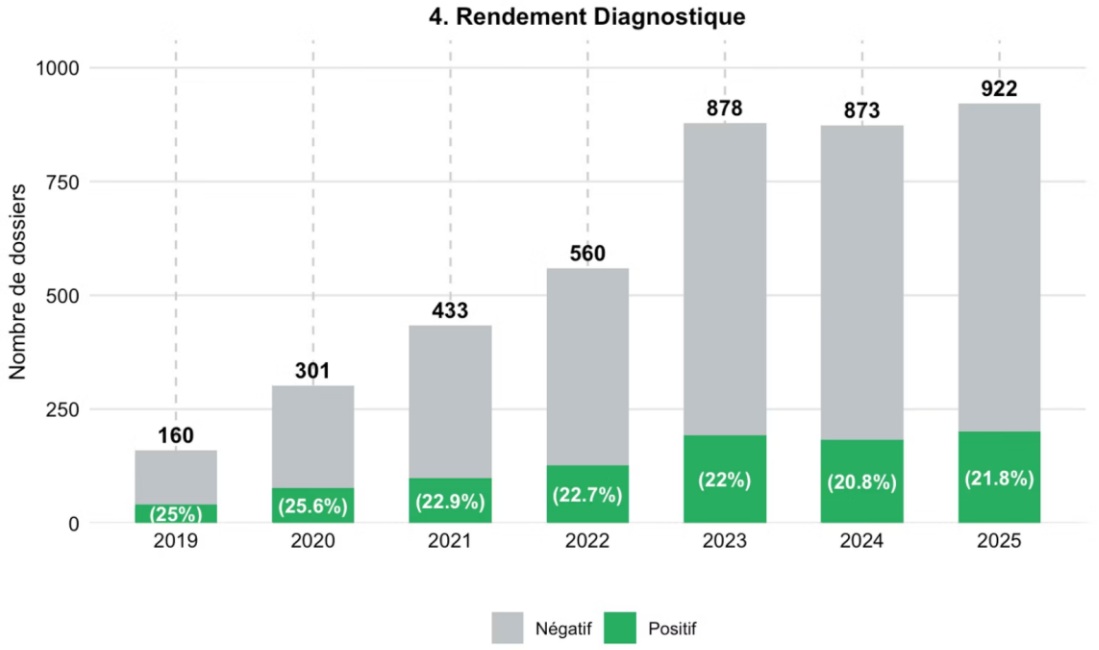
68% AP-HP, mais part du secteur privé (18%) et voire hors région (14%).

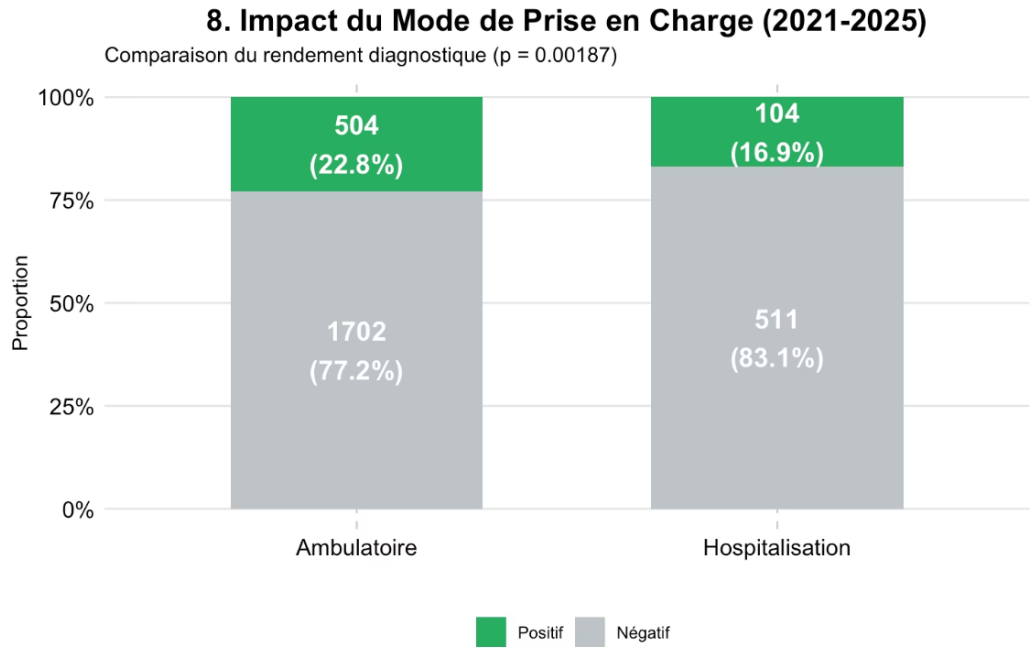






CRMR MARHEA Tenon : Impact Clinique et Volume de Diagnostics depuis 2019





20-25%

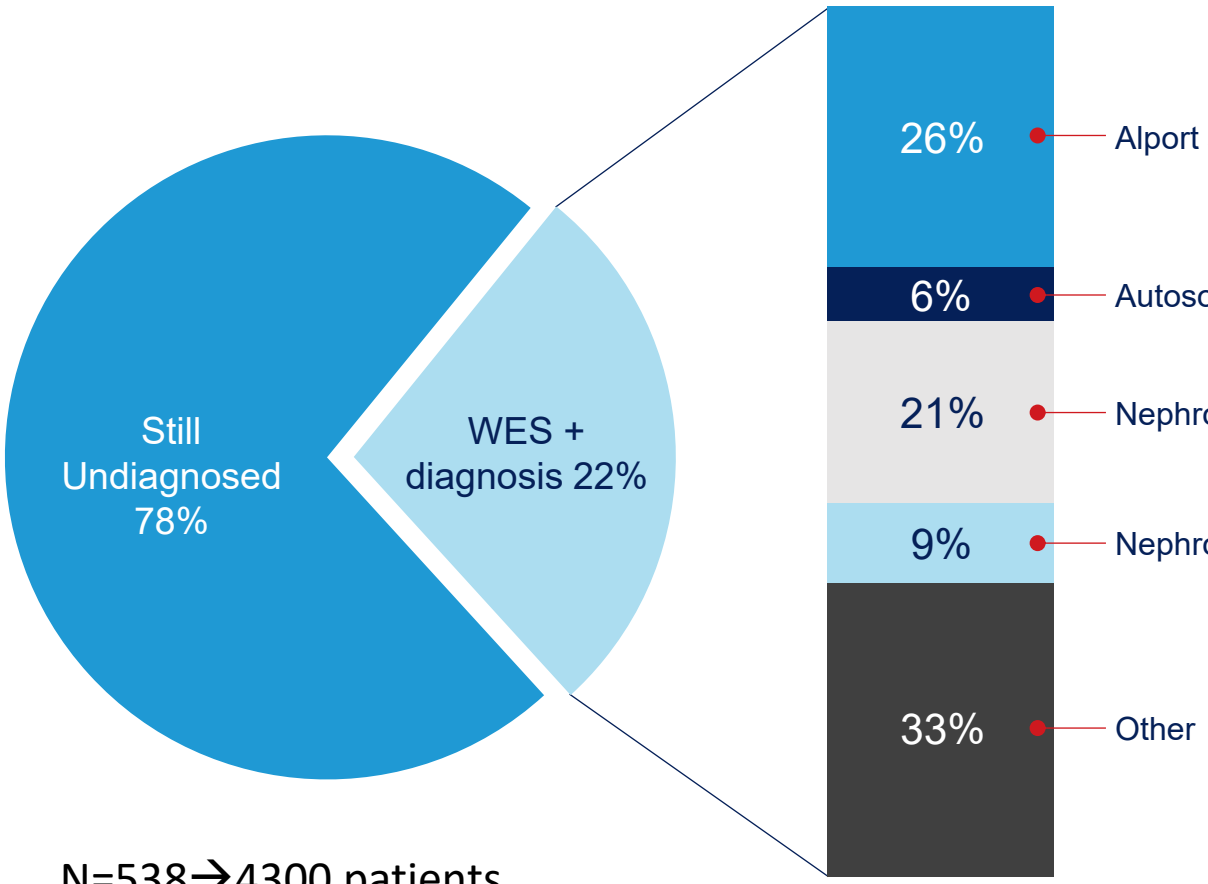
Rendement Diagnostique

~200

Patients Diagnostiqués par an

Un taux de succès élevé pour identifier l'étiologie moléculaire des maladies rénales rare grâce à l’exome.

Diagnostic yield of CKDx in patients with Exome Sequencing at Sorbonne University



Mean age: 43±13 years

80% solo exome

N=538→4300 patients
(Current 2026)

› Kidney Int Rep. 2022 Dec 17;8(3):596-605. doi: 10.1016/j.ekir.2022.12.007. eCollection 2023 Mar.

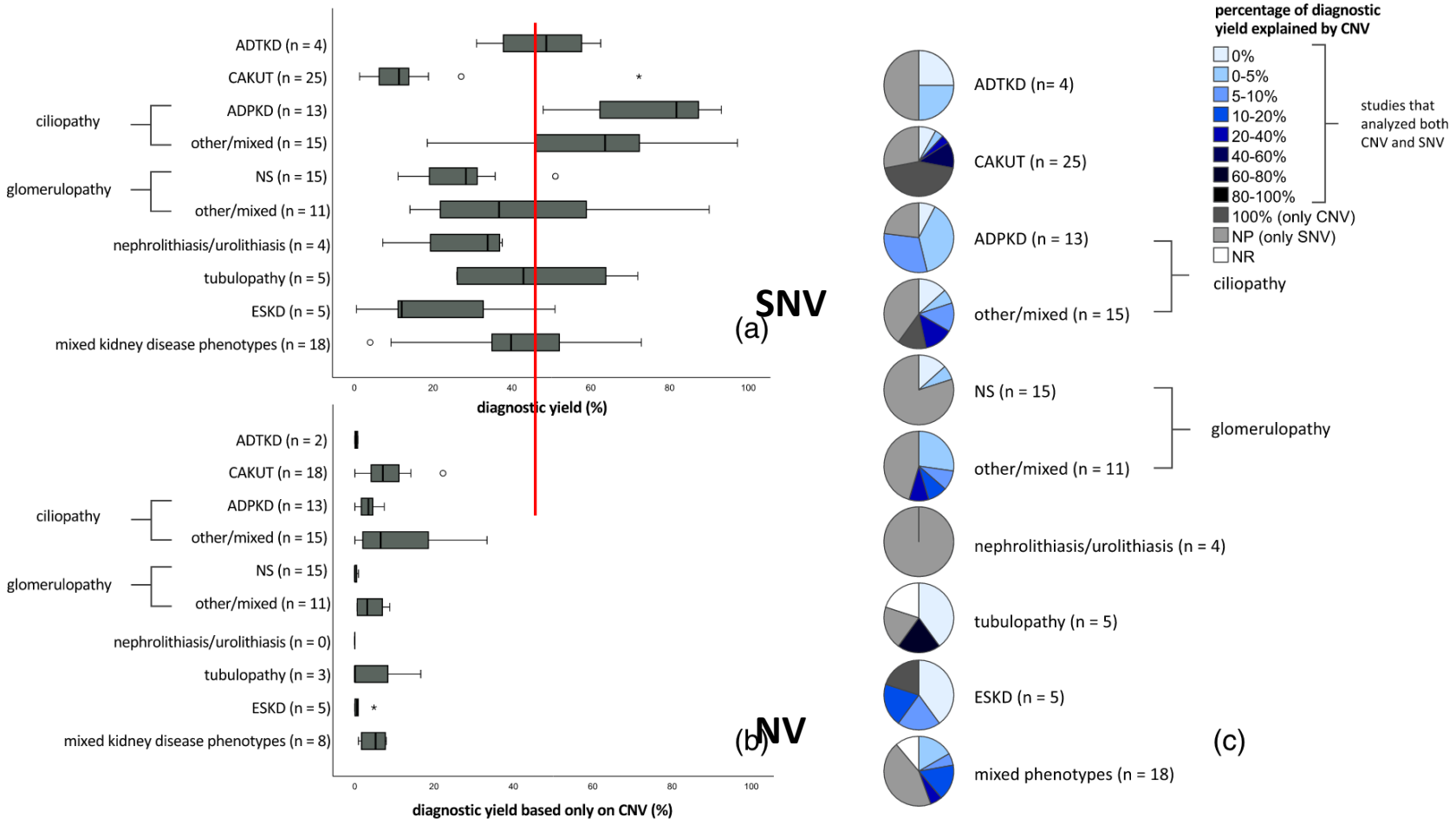
Exome-First Strategy in Adult Patients With CKD: A Cohort Study

Alice Doreille [1 2], Yannis Lombardi [1 2], Marine Dancer [3], Radoslava Lamri [3], Quentin Testard [3], Xavier Vanhoye [3], Anne-Sophie Lebre [4 5], Hugo Garcia [1], Cédric Rafat [1], Nacera Ouali [1], Yosu Luque [1 2], Hassan Izzedine [6], Emmanuel Esteve [2 7], Alexandre Cez [7], Camille Petit-Hoang [1], Hélène François [1 2 8], Armance Marchal [2 7], Emmanuel Letavernier [2 7 8], Véronique Frémeaux-Bacchi [9], Jean-Jacques Boffa [2 7 8], Eric Rondeau [1 2 8], Laure Raymond [3], Laurent Mesnard [1 2 8 10 11]

Affiliations + expand

PMID: 36938085 PMCID: PMC10014383 DOI: 10.1016/j.ekir.2022.12.007

2022 Review of genetic testing in kidney disease patients: Diagnostic yield evaluated across and within kidney phenotype groups



Kidney Transplant waiting list:

12.5-24.5% diagnostic yield

Claus et al. Am J Med Genet. 2022;190C:358–376.

French National data: Sorbonne does at least 25% of the French activity in 2024

ID ABM	INDICATIONS (THESAURUS)	2022	2023	2024
244	CAKUT — Congenital Anomalies of the Kidney and Urinary Tract	511	187	431
245	Ciliopathy excluding PKD	546	167	230
246	Fetal kidneys with hyperechogenicity	see 245 association	88	81
247	Autosomal dominant cystic nephropathies + PKD	707	1405	1845
248	ADTKD — Autosomal Dominant Tubulointerstitial Kidney Disease	see 247 association	277	509
249	Proteinuria + steroid-resistant nephrotic syndrome (SRNS)	222	153	558
250	Familial hematuric nephropathy	273	125	565
251	Complement susceptibility factors for atypical HUS (aHUS)	100	409	166
252	Susceptibility factors for complement-dependent glomerular diseases	same as 251	51	57
253	Urolithiasis or nephrocalcinosis	no data	401	921
254	Tubulopathy	725	458	640
255	Undetermined nephropathy with kidney failure	no data	2004	3953
TOTAL	—	**3084**	**5725**	**9956**

Noticeable impact on patient management following exome sequencing in CKD[1]

78%
clarification of mode of inheritance (n=104)

64%
cascade screening in relatives (n=85)

7%
impact on related living donors (n=10)

11%
handling immunosuppressive therapy or drug (n=15)

20%
rule out recurrence on the graft (n=27)

36%
reverse phenotyping and complementary exams (n=48)

Doreille A, et al. 2022 Dec 17;8(3):596-605

ORIGINAL ARTICLE - CLINICAL RESEARCH

A Clinical Workflow for Cost-saving High-rate Diagnosis of Genetic Kidney Diseases

Becherucci, Francesca[1,2,a]; Landini, Samuela[3,*]; Palazzo, Viviana[3,*]; Cirillo, Luigi[1,2,*]; Raglianti, Valentina[1,2]; Lugli, Gianmarco[1,2]; Tiberi, Lucia[2,3]; Dirupo, Elia[3]; Bellelli, Stefania[4]; Mazzierli, Tommaso[1]; Lomi, Jacopo[1]; Ravaglia, Fiammetta[5]; Sansavini, Giulia[5]; Allinovi, Marco[6]; Giannese, Domenico[7]; Somma, Chiara[8]; Spatoliatore, Giuseppe[9]; Vergani, Debora[3]; Artuso, Rosangela[3]; Rosati, Alberto[9]; Cirami, Calogero[6]; Dattolo, Pietro Claudio[8]; Campolo, Gesualdo[5]; De Chiara, Letizia[2]; Papi, Laura[2]; Vaglio, Augusto[1,2]; Lazzeri, Elena[2]; Anders, Hans-Joachim[10]; Mazzinghi, Benedetta[1]; Romagnani, Paola[1,2,a]

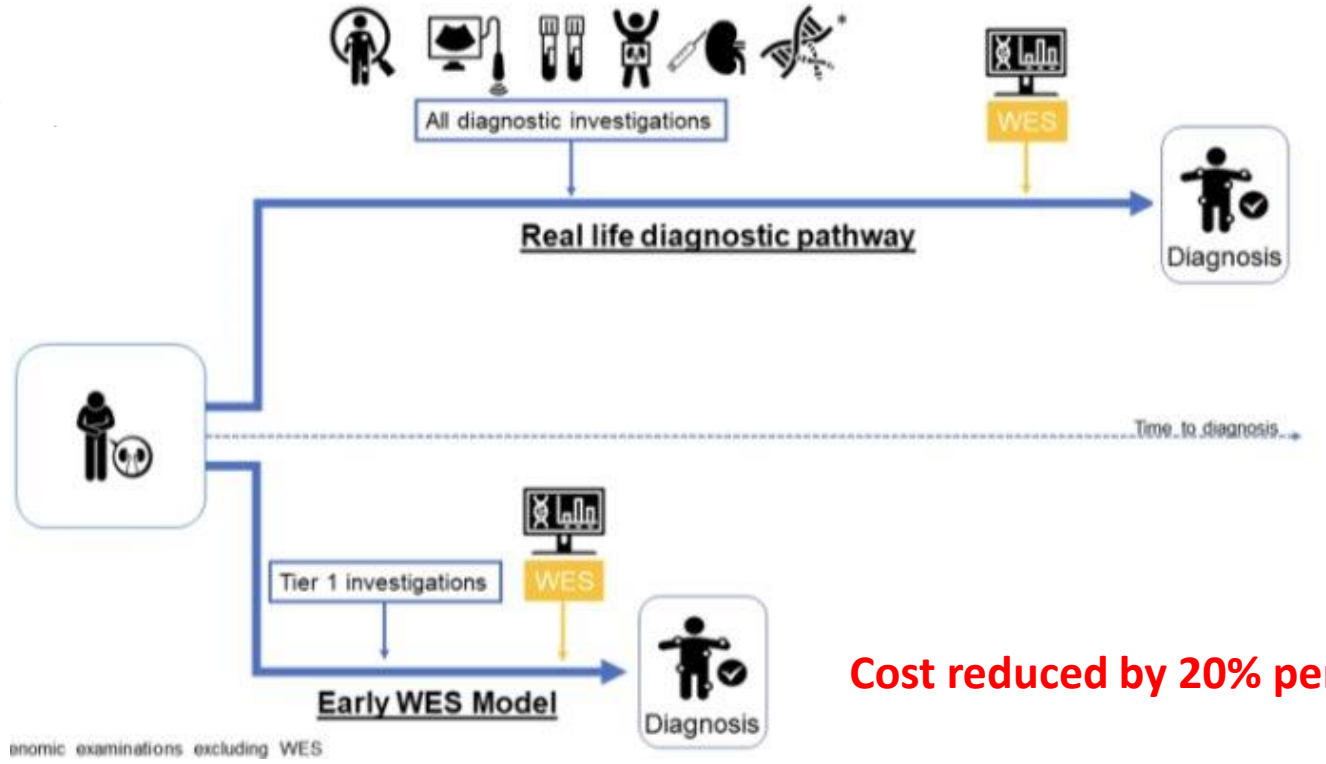
Author Information

Journal of the American Society of Nephrology

2023

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

476 patients (156 adults)



Cost reduced by 20% per patient

By doing genomics first-hand we save money !

We developed a predictive model for WES positivity to guide clinical decision-making.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

SORBONNE UNIVERSITÉ

Inserm

Predictive score for exome positivity for Adult's Nephropathies

1. Age (in years): 45

2. Current CKD stage III, IV or V: Yes ◉ No ○

3. First-degree history of kidney disease*: Yes ◉ No ○

4. Current diagnosis based on clinical presentation:

Vascular disease ○

Glomerular disease ○

Tubulo-interstitial disease ○

Undiagnosed/isolated hem. or prot./other ○

Dev. disorders/unclassic cystic disease ◉

Submit

Source: *Exome-first strategy in adult patients with chronic kidney diseases. Alice Doreille, et al. Submitted.*

Not externally validated, for exploratory purposes only. *Please notice that the absence of a family history of kidney disease does not preclude the absence of a genetically-related kidney disease

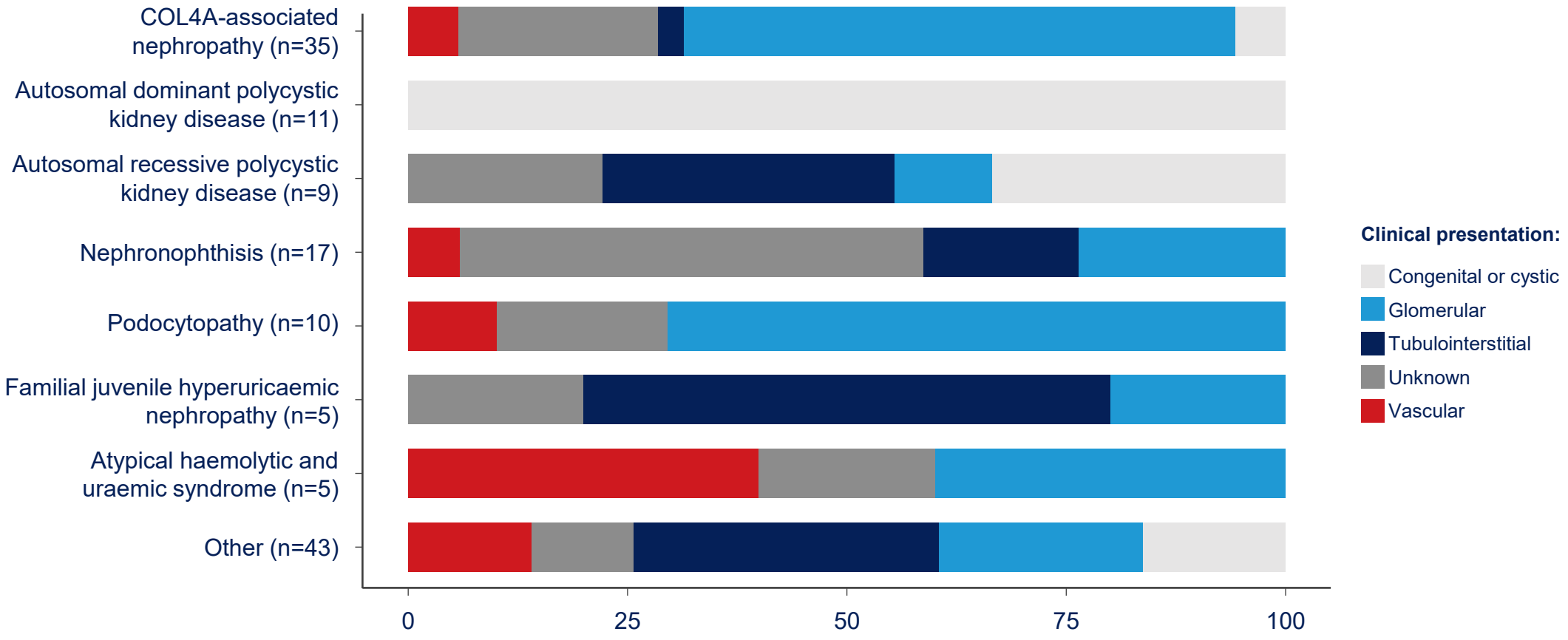
The pre-test probability of positive result is **65.23%.**

Area under the curve in internal validation (n=497 index cases): 0.726 [95% confidence interval: 0.670-0.782]. Not externally validated, for exploratory purposes only.

Back to calculator.

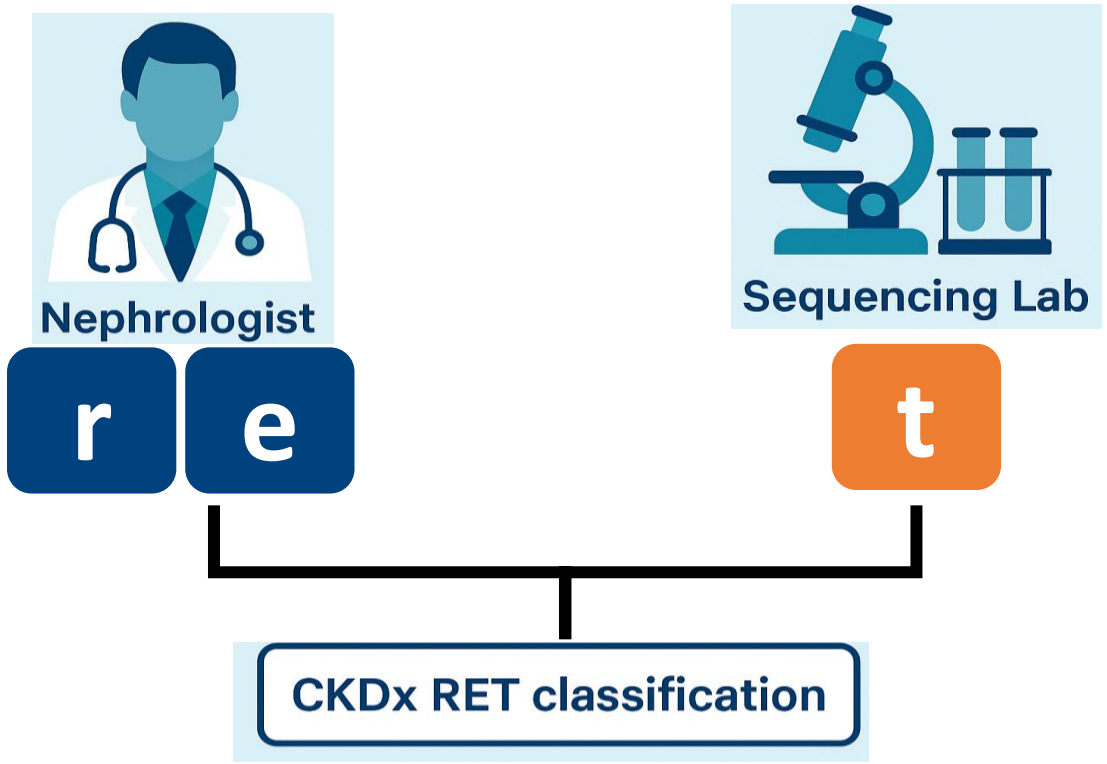
Doreille A, et al. 2022 Dec 17;8(3):596-605

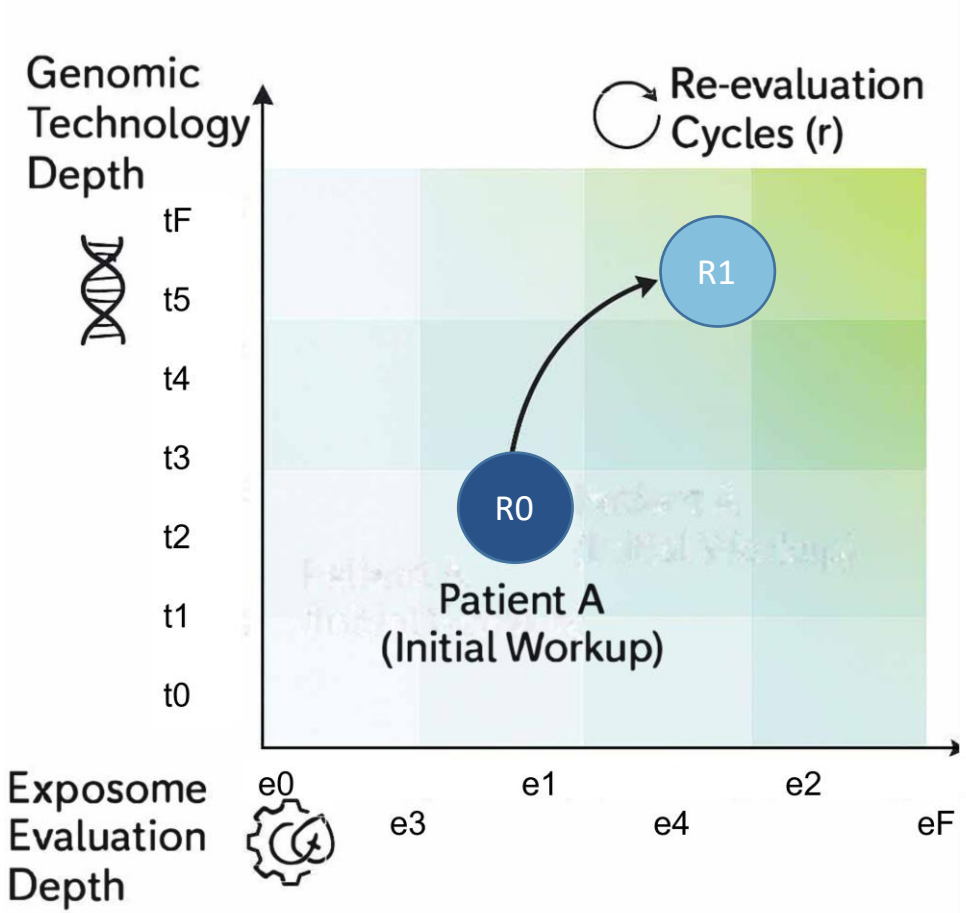
Large diagnostic heterogeneity, clinics is misleading[1], Still 75% of CKDx do not reach a molecular diagnosis !



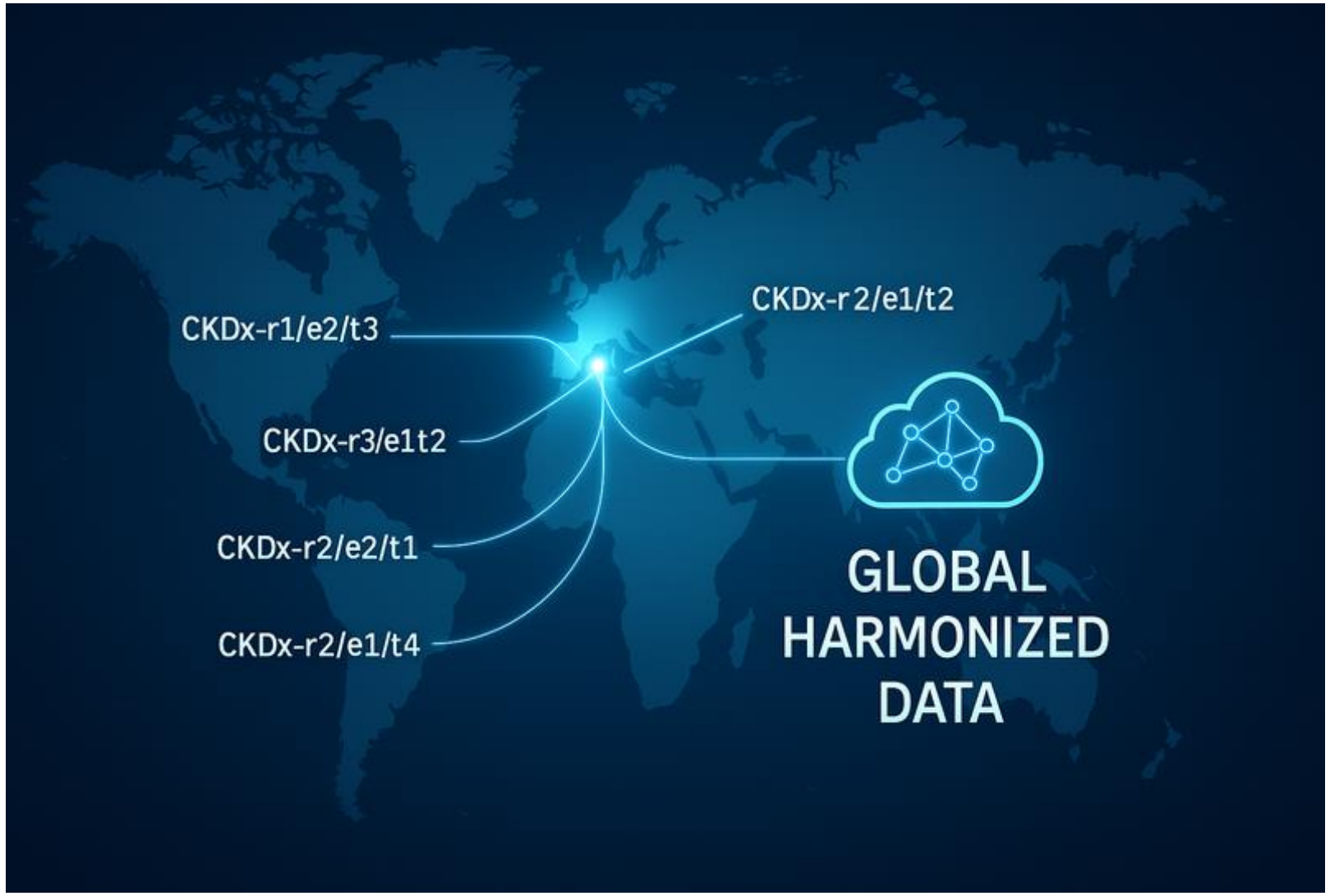
Doreille A, et al. 2022 Dec 17;8(3):596-605

The 2025 Collaborative Sorbonne classification for CKDx





The value of sharing exposomic, genomic, and phenotypical data across registries to solve CKDx



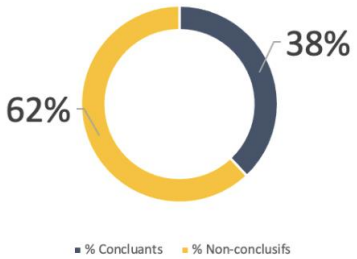
Data
Structured

Dynamic

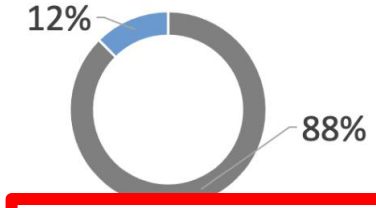
Fair Principles

YouTube

RENDEMENT DIAGNOSTIQUE GLOBAL



TYPE DE VARIATIONS RENDUES



105

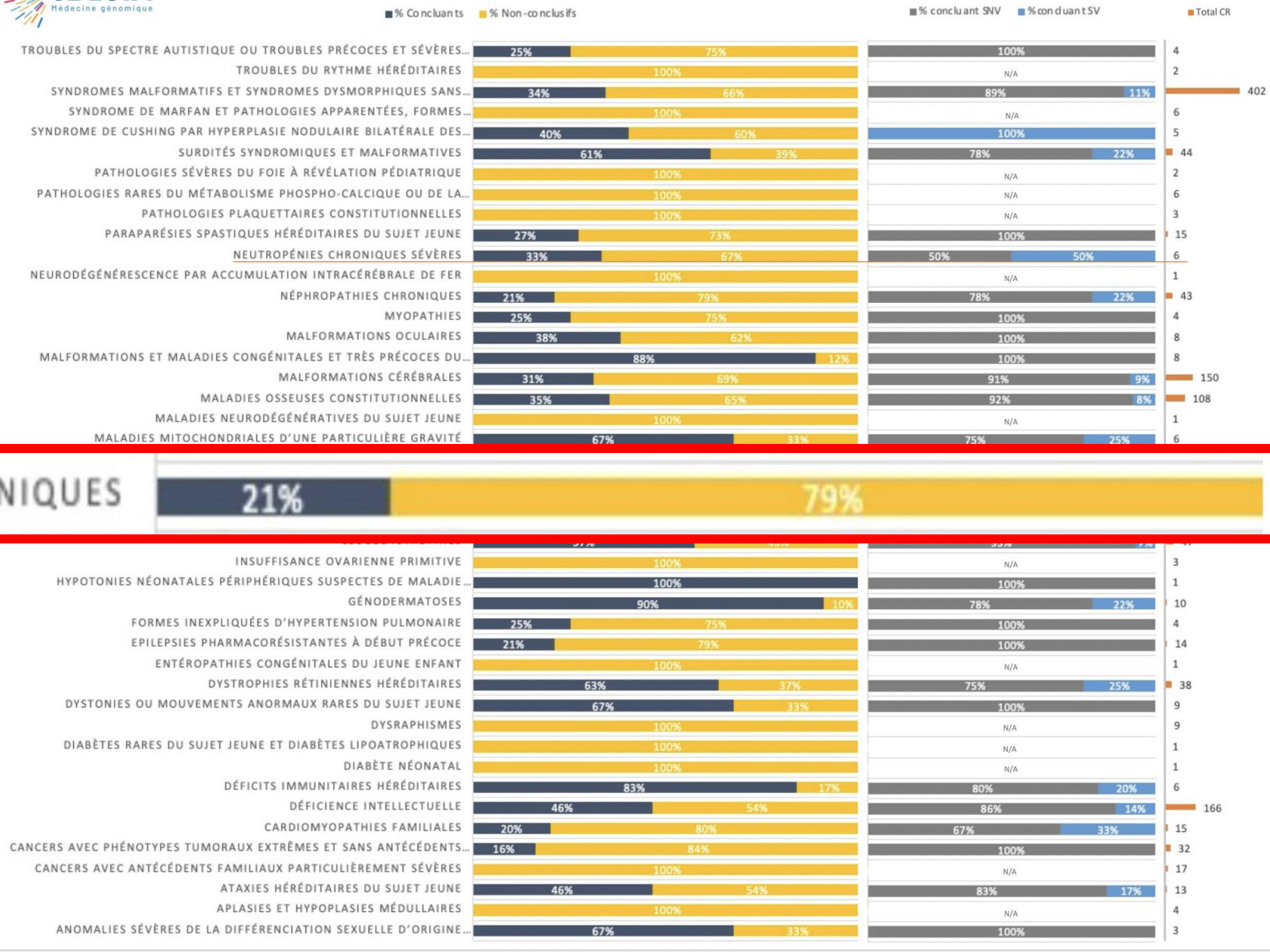
BIOLOGISTES SIGNATAIRES

1262

COMPTE-RENDUS

SEQOIA Médecine génomique

RENDEMENT DIAGNOSTIQUE / PRE-INDICATION

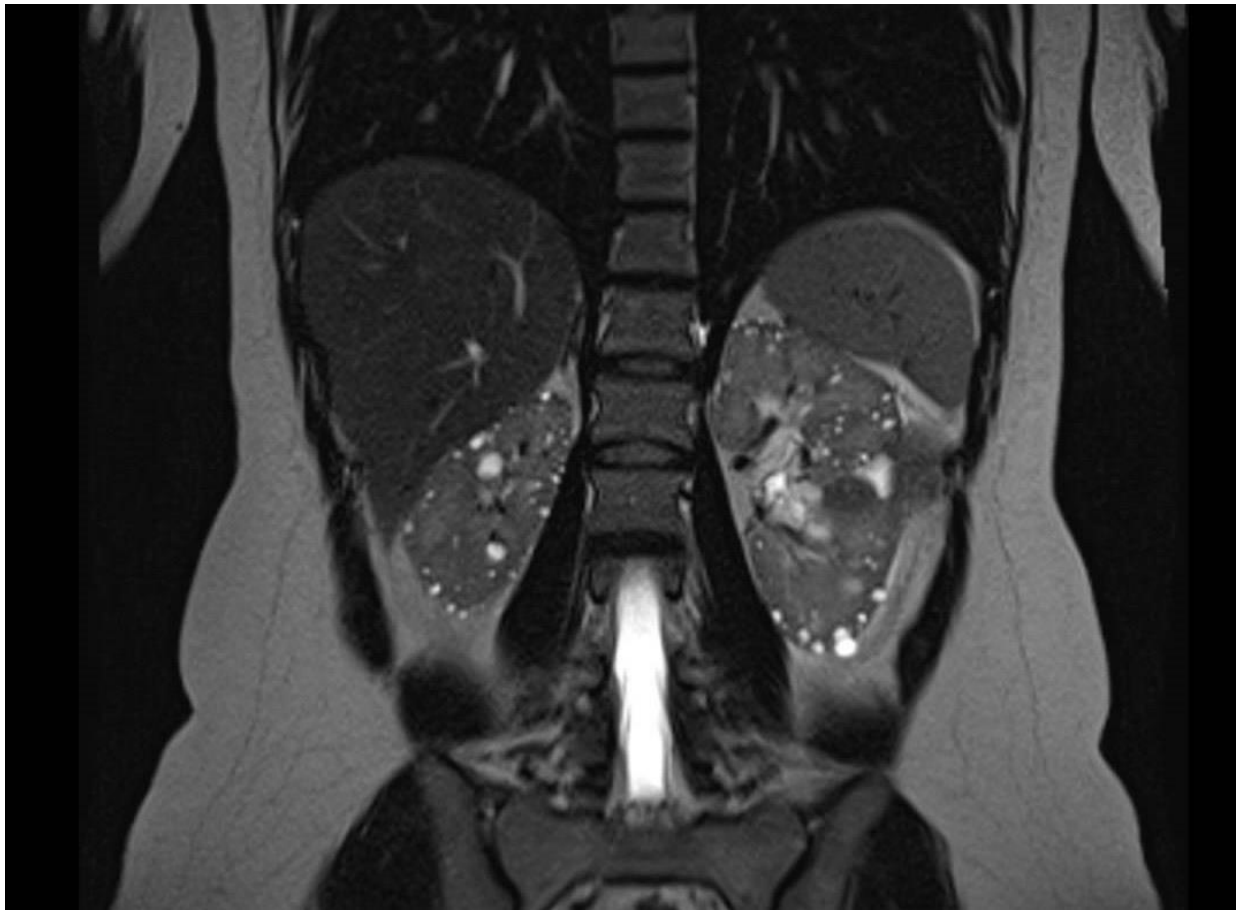


NÉPHROPATHIES CHRONIQUES 21% 79%

Example of diagnosis saved by WGS on the top of WES

Clinical case 1

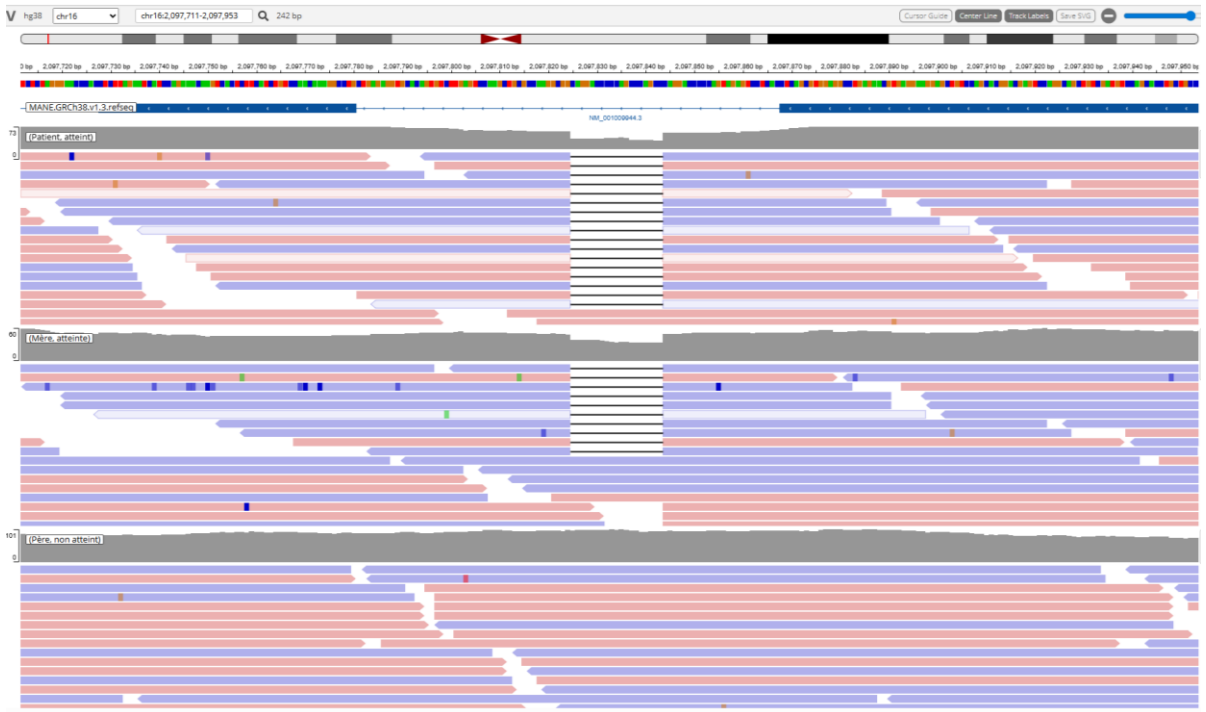
26-year-old female patient: multicystic kidneys with a hepatic microcyst and cerebral aneurysm. Mother and older sister affected. Exome sequencing identified a pathogenic COL4A4 variant, which does not fully explain the phenotype. Trio genome sequencing with parents planned.

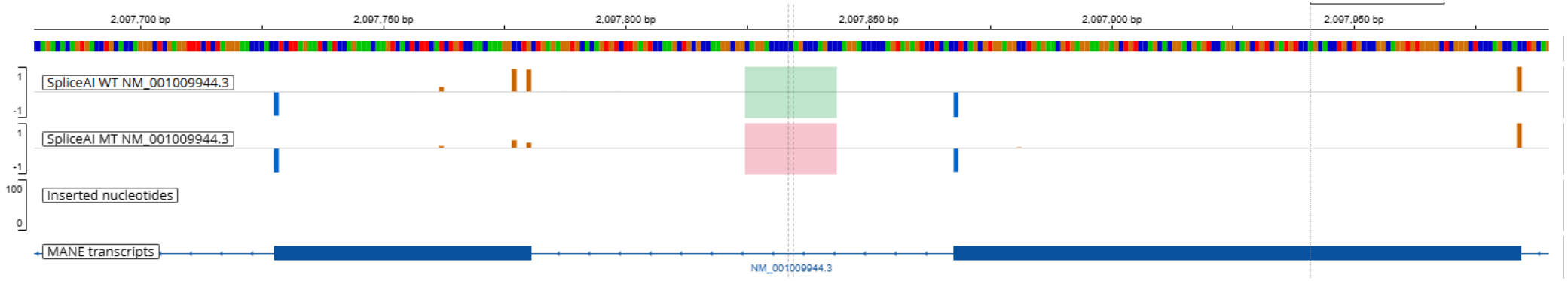


Example of diagnosis saved by WGS on the top of WES

Clinical case 1

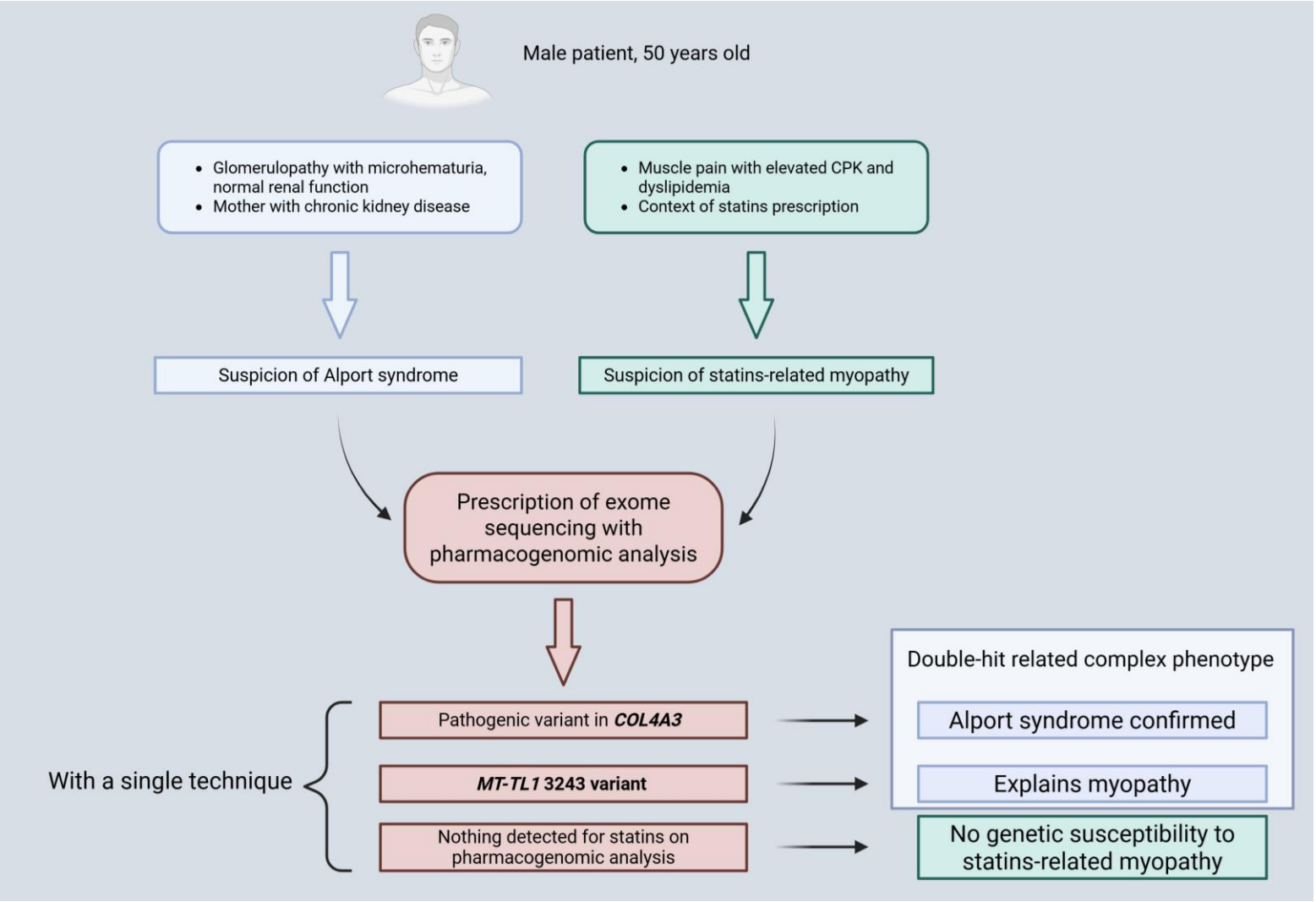
- **Identification of an intronic heterozygous deletion of 18nt in the *PKD1 gene missed by WE***
- **NM_001009944.3:c.10167+25_10167+43del**





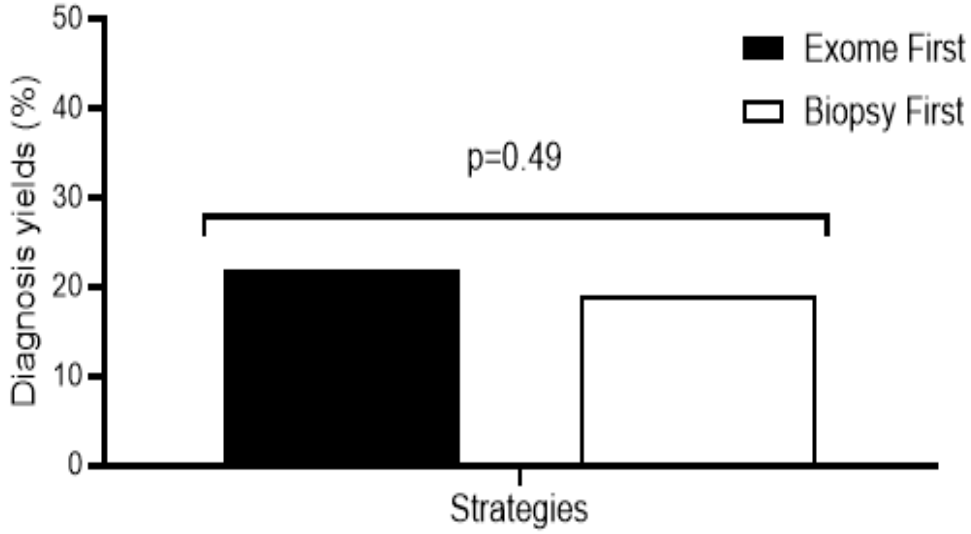
The value of Pharmacogenomics and WES combined

Clinical case 2

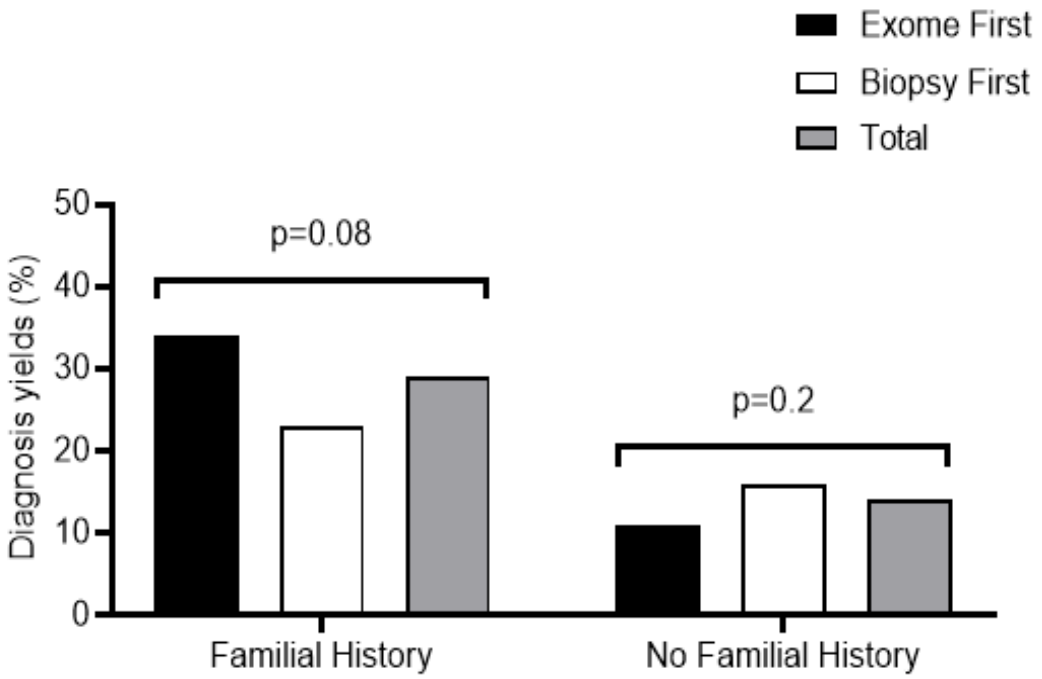


The Exome first vs kidney biopsy first

23% 19%



Similar diagnostic yield



Kidney biopsy = WES First

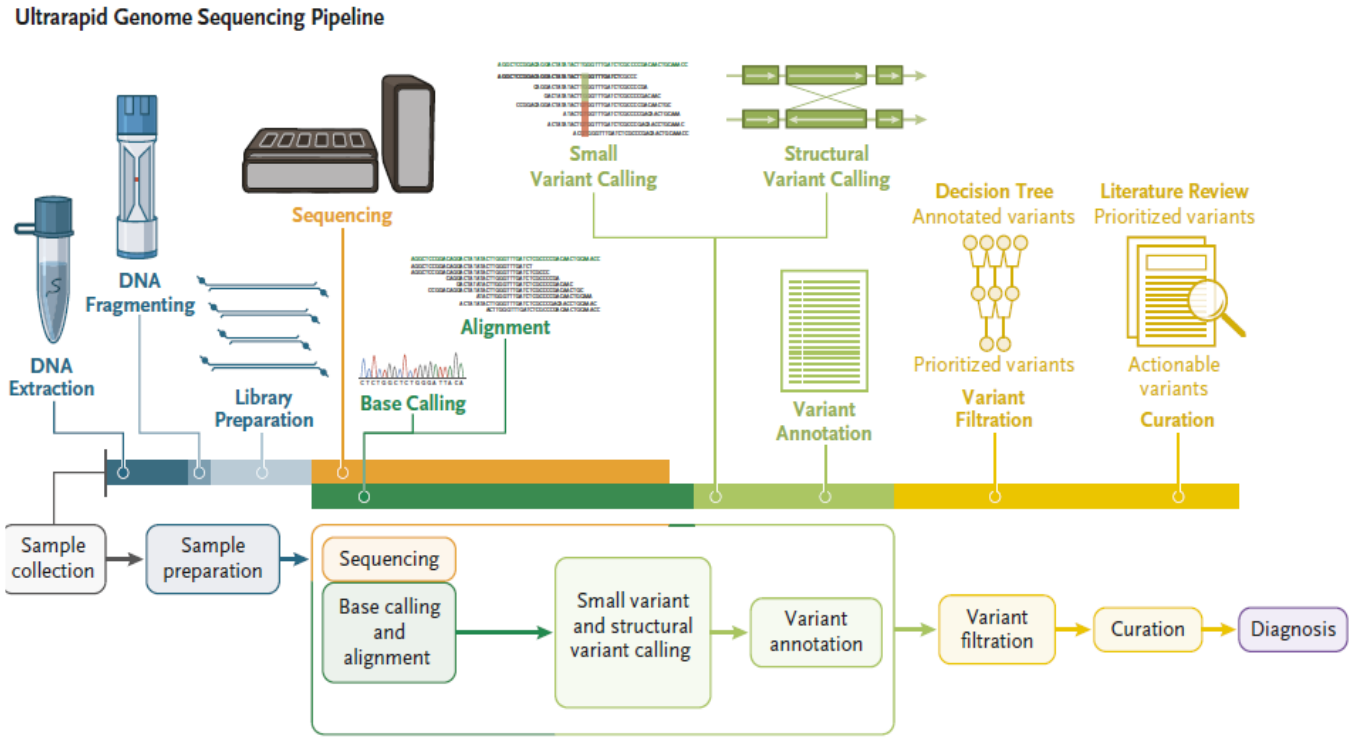
Vedrine et al, 2026, manuscript in Review

ultrafast/rapid medical genomics

NEJM THIS WEEK

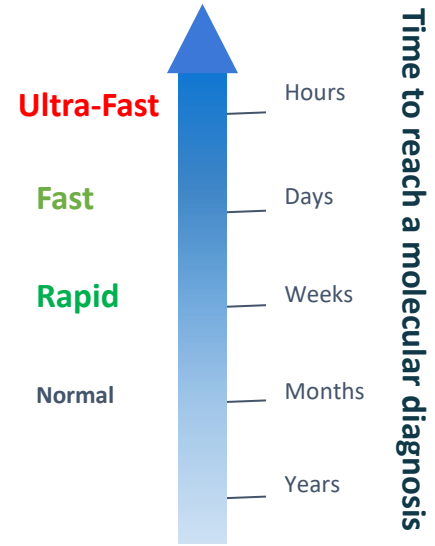
Ultrarapid Nanopore Genome Sequencing in a Critical Care Setting

N Engl J Med 2022; 386:700-702



In 2022 Nanopore technology demonstrated that we can fall below 8 Hours for human whole genome analysis

New Taxonomy of sequencing



Different pace of genetic diagnoses for early intervention

ultrafast/rapid medical genomics

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Broad Clinical Labs sets new GUINNESS WORLD RECORDS™ title for fastest DNA sequencing technique

Whole human genome sequencing and analysis was completed in less than 4 hours, surpassing the previous benchmark of 5 hours and 2 minutes.

By Broad Clinical Labs

October 15, 2025

Credit: Anna Olivella Photography

Michael Empric, official adjudicator Broad Clinical Labs with a certificat

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Toward Same-Day Genome Sequencing in the Critical Care Setting

TO THE EDITOR: Rapid genetic diagnosis is increasingly used in critical care management, particularly in neonatal intensive care units (NICUs).[1-3] However, many critical care decisions occur on the scale of hours, whereas current options for clinically available rapid genomic sequencing take days (from sample receipt to re-

We piloted this method in a cohort of infants in a NICU to investigate its feasibility and capacity to produce results that align with urgent critical care workflows.

Over the course of 3 weeks, we sequenced and analyzed 15 human genomes (1 or 2 per day) on the prototype of sequencing by expan-

Advances in kidney transplantation: The allogenomics concept

Allogenomics

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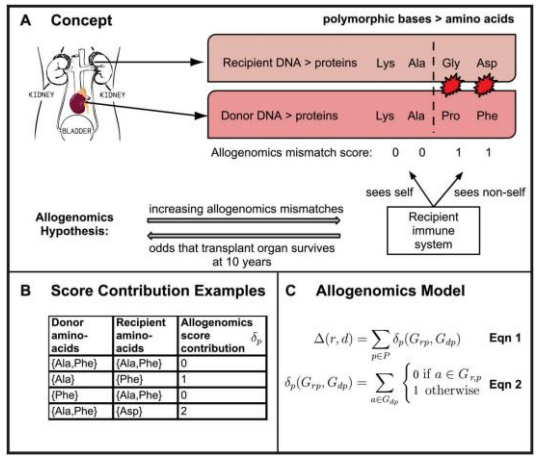


Donor amino-acids	Recipient amino-acids	Allogenomics score contribution δ_p
{Ala,Phe}	{Ala,Phe}	0
{Ala}	{Phe}	1
{Phe}	{Ala,Phe}	0
{Ala,Phe}	{Asp}	2

$$\Delta(r,d) = \sum_{p \in P} \delta_p(G_{rp}, G_{dp}) \quad \text{Eqn 1}$$

$$\delta_p(G_{rp}, G_{dp}) = \sum_{a \in G_{dp}} \begin{cases} 0 \text{ if } a \in G_{rp} \\ 1 \text{ otherwise} \end{cases} \quad \text{Eqn 2}$$

About AlloPipe

We are open source!
AlloPipe is available from
https://github.com/huguesrichard/Allopipe

The allogenomics.com webserver is based on AlloPipe, which is a computational tool designed for **large- scale genomic comparisons between two human samples.** The AlloPipe tool has been developed in the context of transplantation - whether Solid Organ Transplantation (SOT) or Haematopoietic Cell Transplantation (HCT). From high throughput sequencing data - such as Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) - AlloPipe first returns the **directional amino acid missmatches potentially triggering indirect alloreactivity** :

- **after solid organ transplantation**: directional amino acid missmatches of interest are the ones present by the donor but absent by the recipient, i.e. triggerring the recipient's immune system
- **after allogeneic haematopoietic cell transplantation**: directional amino acid missmatches of interest are the ones present by the recipient but absent by the donor, i.e. triggerring the donor's immune system

Genomics might restratify graft attribution or transplant risk

Using rapid genomics for precision medicine in intensive care in nephrology at Tenon Hospital

TO THE EDITOR:

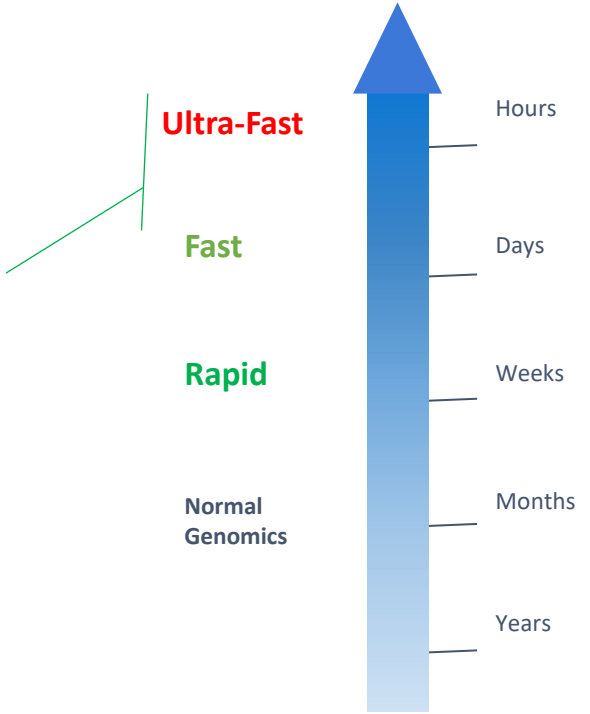
Genomic analysis of adult thrombotic microangiopathies in less than 3 days: from rapid to fast genomics to treatment

Nadhir Yousfi,[1,*] Cyril Mousseaux,[1-4,*] Abderaouf Hamza,[5] Pierre Laville,[1,6] Marie Mille,[7] Nicolas Philippe,[7] Marine Dancer,[5] Christophe Bouder,[8] Yosu Luque,[1-4] Cédric Rafat,[1,2,4] and Laurent Mesnard[1-4,9,10]

[1]Unité Mixte de Recherche S1155, INSERM, Sorbonne Université, Paris, France; [2]Service de Soins Intensifs Néphrologiques et Rein Aigu, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France; [3]Faculté de Médecine, Sorbonne Université, Paris, France; [4]French Intensive Care Renal Network, Lyon, France; [5]Department de Génétique, Institut Curie, Paris Science et Lettres Université, Paris, France; [6]Eurofins Biomnis Laboratory, Lyon, France; [7]SeqOne Genomics, Montpellier, France; and [8]Institut des Systèmes Intélligents et de la Robotique, Centre National de la Recheque Scientifique, [9]Institut des Sciences du Calcul et des Données, and [10]Centre National Référence des Micro-Angiopathies Thrombotiques, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France

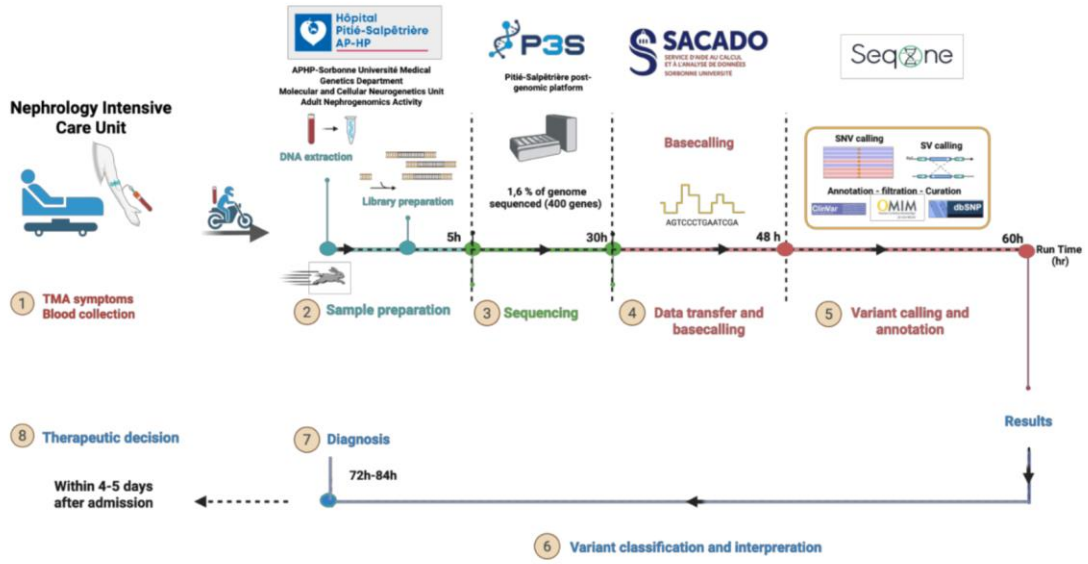
Using nanopore sequencing, we showed the feasibility and impact of rapid genomic screening for managing thrombotic microangiopathies in 18 prospective cases, achieving diagnoses in <3 days. We compared the results with standard exome sequencing, cost efficiency, and complement blockade initiation.

blood® 21 NOVEMBER 2024 | VOLUME 144, NUMBER 21

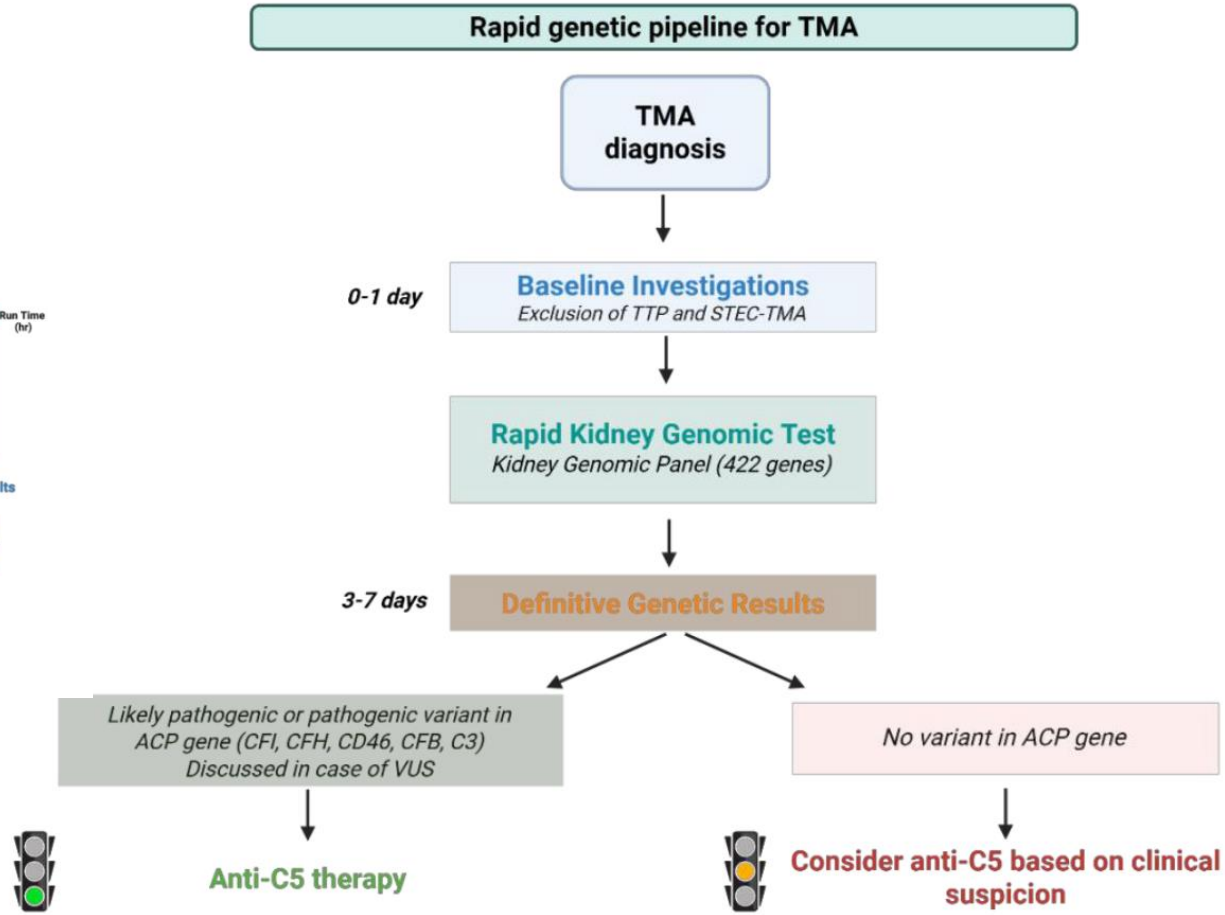


Clinical implementation at since September 2024.

Using rapid genomics for precision medicine in intensive care in nephrology at Tenon Hospital and Sorbonne University



eFigure 1: TMA diagnosis workflow.

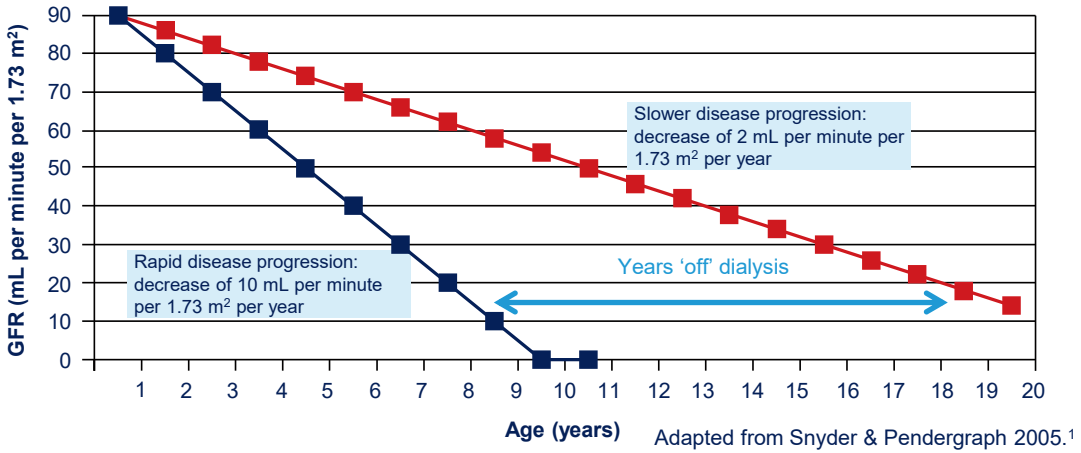


Mousseau et al. Manuscript in Review 2026

Estimated saved cost by APHP in 2025 for 32 patients : 2,055,768 Euros

Beyond the cost, preventive care: An early renal diagnosis might impact the number of years ‘off’ dialysis?

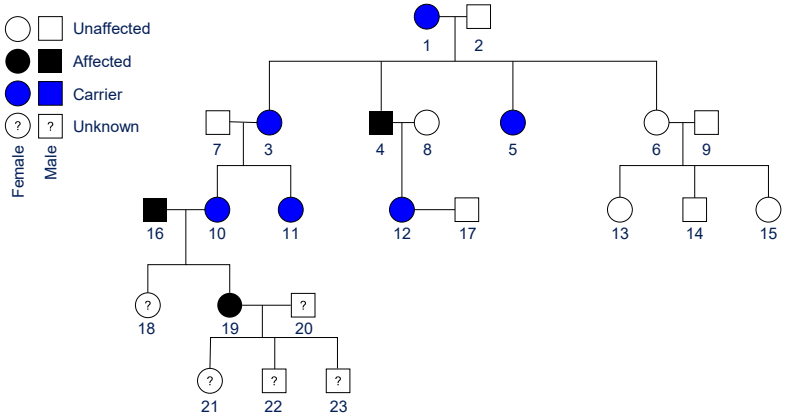
Estimating the time to ESRD using GFR[1]



Adapted from Snyder & Pendergraph 2005.[1]

Leverage: 1 year of dialysis = 65,000–80,000 euros

Detection of early phenotype (co-segregation)



Prevention in relatives ++++
‘Cascade screening’

Nephrogenomics can organize preventive medicine

ESRD, end-stage renal disease; GFR, glomerular filtration rate.

1. Snyder S, Pendergraph B. *Am Fam Physician.* 2005;72(9):1723–1732.

Where the Team is moving toward 2030 and beyond

- **More patients & larger cohort**, more statistical power to find new genes associated with CKDx with new bioinformatics methods (SharkVNTyper, allogenomics..).

- **Precision:** Whole genome “long-Read”, with methylation profiling
  - More tailored medicine, +5% at initial diagnosis, capture of PRS
  - Introducing Polygenetic Risk Score (PRS) for risk stratification

- **Prepare Cure:** associated with molecular data we are accumulating
  - Gene editing with *in situ* (into the kidney only) delivery of genetic constructs that will repair/Edit the altered kidney DNA of the patient

nature reviews nephrology

https://doi.org/10.1038/s41581-025-00970-1

Review article

Check for updates

Nephrogenomics, precision medicine and the role of genetic testing in adult kidney disease management

Ilias Bensouna[1,2], Alice Doreille[3], Marine Dancer[4], Anne-Sophie Lebre[5,6], Thomas Robert[7,8] & Laurent Mesnard[1,2,9,10,11]

Abstract

Genetic investigations in nephrology have long been viewed as the

Sections

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Néphrogénomique Sorbonne

@NéphrogénomiqueSorbonne · 4 abonnés · 4 vidéos

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Abonné

Vidéos

Venir en consultation de néphrogénomique à APHP Sorbonne Université

9 vues • il y a 2 semaines

CKDx is a good start - But we can go further ? (english version)

12 vues • il y a 6 mois

Qu'est ce que la co-ségrégation en génétique ? Avec Nadia Ould Ouali Conseillère en…

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Qu'est ce que la consultation de Néphrogénomique ? Avec le Professeur…

102 vues • il y a 10 mois

https://www.youtube.com/@N%C3%A9phrog%C3%A9nomiqueSorbonne

Patient and professional are welcome to our website

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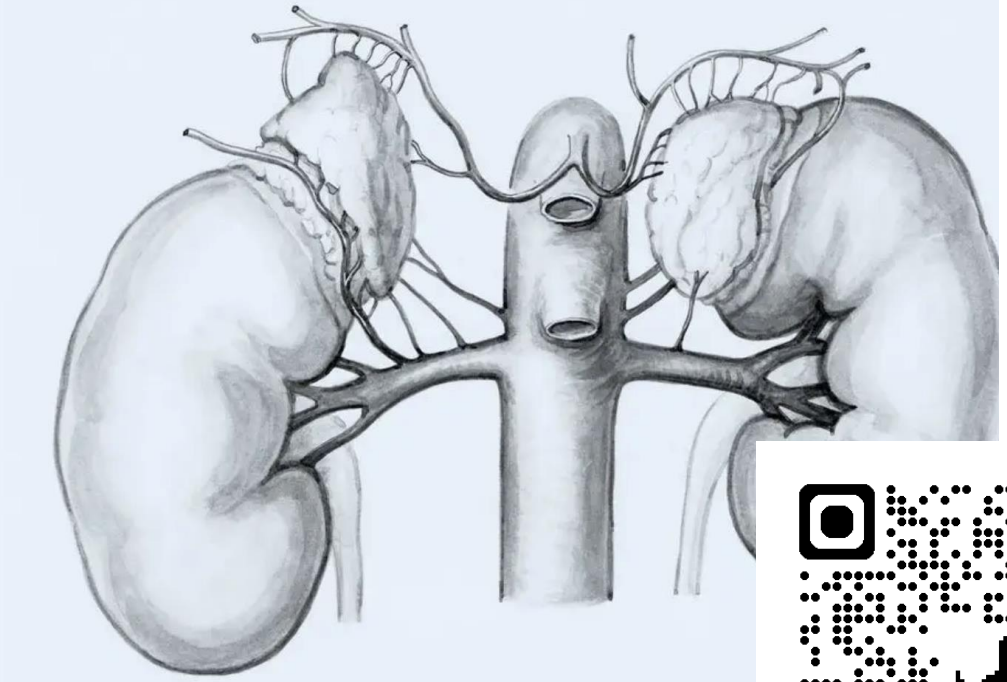
SORBONNE UNIVERSITÉ

Consultation de Néphrogénomique adulte



L'équipe est dirigée par le Professeur Laurent MESNARD et est composée de généticiens cliniciens, néphrologues adultes formés à la génétique, une psychologue et une conseillère en génétique dédiée aux maladies rares du rein de l'adulte. L'équipe interagit avec les consultations et services d'oncogénétique, cardiologie, hématologie pour la prise en charge des découvertes incidentales les plus fréquentes.

Contactez-nous

Découvrir les maladies

https://www.nephrogenomics.com/

Many Thanks to

Colleagues from AP-HP & Sorbonne University & beyond

AP-HP: **Delphine Heron**, **Eric Leguern**, **Eric Rondeau, Anne-Sophie Lebre, Alice Doreille, Yannis Lombardi, ilias Bensouna, Nadia Ould Ouali, Mathieu Georget.**

Nadhir Yousfi, Abderaouf Hamza, V.Frémeaux-Bacchi

Colleagues from Biomnis Lyon

Laure Raymond, Marine Dancer Radoslava Lamri, Mohamed Taoudi, Jean-Francois Taly, Mélanie Eyries,

ORKID and MARIH: French networks for rare diseases