Mesure du débit de filtration glomérulaire

Dr Pierre Delanaye
Université de Liège
CHU Sart Tilman
Belgique

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Et si on mesurait le DFG…

Mesurer le DFG: Pourquoi?
Une question de précision!

- Décision d'initier la dialyse
- Individus sarcopéniques
- Gabarit extrême
- Cirrhose, USI
- Hyperfiltration

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, 14, p1861

The GFR and GFR decline cannot be accurately estimated in type 2 diabetics

Flavio Gaspari[1,7], Piero Ruggenenti[1,2,7], Esteban Porrini[1,3,7], Nicola Motterlini[1], Antonio Cannata[1], Fabiola Carrara[1], Alejandro Jiménez Sosa[3], Claudia Cella[1], Silvia Ferrari[1], Nadia Stucchi[1], Aneliya Parvanova[1], Ilian Iliev[1], Roberto Trevisan[4], Antonio Bossi[5], Jelka Zaletel[6] and Giuseppe Remuzzi[1,2]; for the GFR Study Investigators

[1]Clinical Research Center for Rare Diseases 'Aldo & Cele Daccò', Mario Negri Institute for Pharmacological Research, Bergamo, Italy; [2]Unit of Nephrology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [3]Research Unit, Hospital Universitario de Canarias, Tenerife, Spain; [4]Unit of Diabetology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [5]Unit of Diabetology, Treviglio Hospital, Treviglio, Italy and [6]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center, Ljubljana, Slovenia

- **Type 2 diabetics**
- **Iohexol**
- **n=600**
- **Hyperfiltration (DFG>120 mL/min/1.73 m²) n=90**
- **CKD (<80 mL/min/1.73 m²) n=76**

	Accuracy		Bias		Precision	
	30%		Mean		SD	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
All	85	91	-16	-13	17	16
Normofiltrating (80-120 mL/min/1.73 m²) N=434	88	96	-15	-11	14	12
Hypofiltrating (lower than 80 mL/min/1.73 m²) N=76	88	82	+0.6	+4	16	16
Hyperfiltrating (over 120 mL/min/1.73 m²) N=90	68	77	-33	-33	18	13

On rate tous les diagnostics d'hyperfiltration !

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Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, 14, p1861

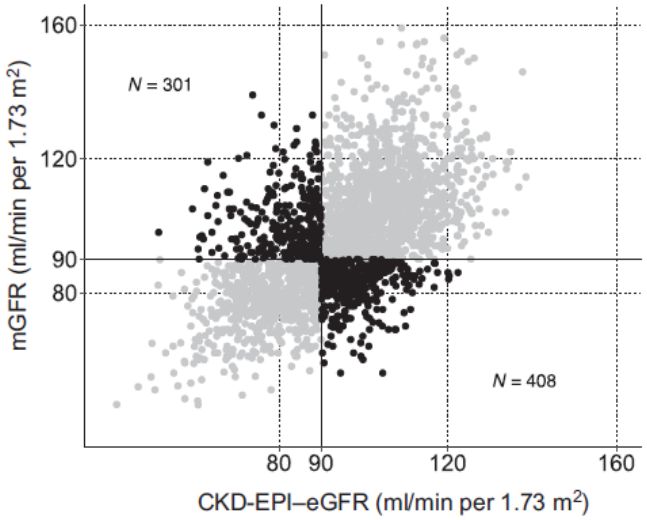
Impact of estimation versus direct measurement of predonation glomerular filtration rate on the eligibility of potential living kidney donors

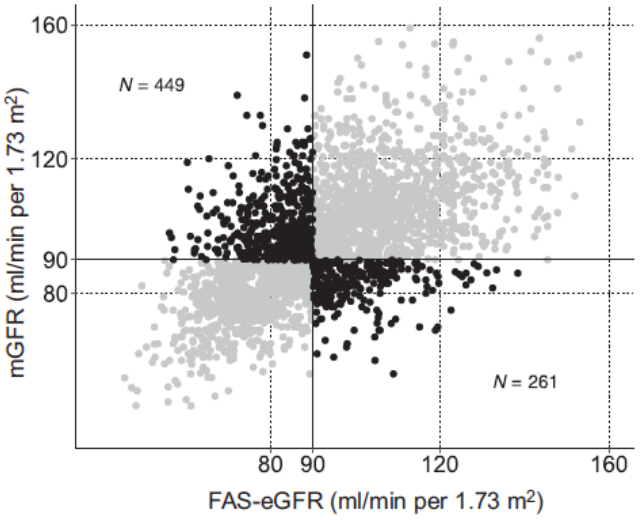
see commentary on page 738

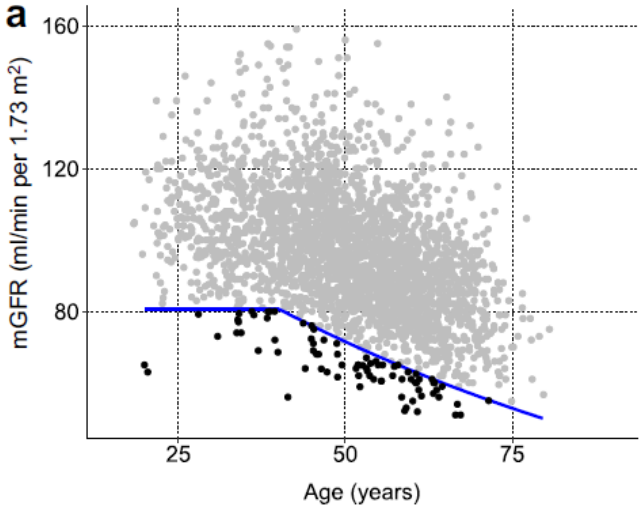
François Gaillard[1,2], Marie Courbebaisse[2,3], Nassim Kamar[4,5,18], Lionel Rostaing[6,18], Lola Jacquemont[7,8], Maryvonne Hourmant[7,8], Arnaud Del Bello[4], Lionel Couzi[9,10], Pierre Merville[9,10], Paolo Malvezzi[6], Benedicte Janbon[6], Bruno Moulin[11], Nicolas Maillard[12], Laurence Dubourg[13,14], Sandrine Lemoine[13], Cyril Garrouste[15], Hans Pottel[16], Christophe Legendre[1,2], Pierre Delanaye[17,19] and Christophe Mariat[12,19]

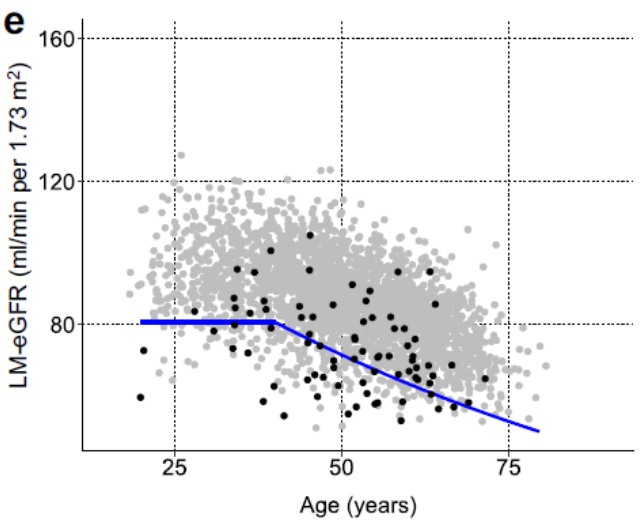
Kidney International (2019) **95,** 896–904;

- N=2,733 donneurs potentiels
- DFG mesuré, créatinine calibrée


160
120
90
80
N = 301
N = 408
mGFR (ml/min per 1.73 m²)
80 90 120 160
CKD-EPI–eGFR (ml/min per 1.73 m²)


160
120
90
80
N = 449
N = 261
mGFR (ml/min per 1.73 m²)
80 90 120 160
FAS-eGFR (ml/min per 1.73 m²)


a
160
120
80
mGFR (ml/min per 1.73 m²)
25 50 75
Age (years)


e
160
120
80
LM-eGFR (ml/min per 1.73 m²)
25 50 75
Age (years)

Mesurer le DFG: Pourquoi?
Une question de précision!

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- Individus sarcopéniques
- Gabarit extrême
- Cirrhose, USI, Hyperfiltration
- Donneur vivant
- Dosage d'un médicament potentiellement néphrotoxique (=>2)
- Recherche Clinique, EMA

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, 14, p1861

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/83874/2014
Committee for Medicinal Products for Human use (CHMP)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

5.2. Measures of renal function

In order to have a reference measure of renal function that is independent of clinical practice at the time of conduct of the pharmacokinetic study, it is recommended that a method accurately measuring GFR using an exogenous marker is used to determine renal function in the subjects in the pharmacokinetic study, if possible.

Mesurer le DFG: Pourquoi?
Une question de précision!

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- Individus sarcopéniques
- Gabarit extrême
- Cirrhose, USI, Hyperfiltration
- Donneur vivant
- Dosage d'un médicament potentiellement néphrotoxique (=>2)
- Recherche Clinique, EMA
- Pas de preuve définitive…

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, 14, p1861

Différents marqueurs
Mais comment faire?

- Clairance urinaire

- Clairance plasmatique

Clairance urinaire

- Infusion constant, marqueur à l'équilibre
- Mesure plasmatique et urinaire du marqueur
- Collecter les urines (toutes les 30 ou 60 minutes) et mesure du débit urinaire
- Répéter 3 ou 4 fois
- Cl = [U] x [V]/ [P] (moyenne des 3 collections)

Clairance plasmatique = Dose / AUC

Théoriquement, α and β doivent être calculés

↓

Pas simple en pratique

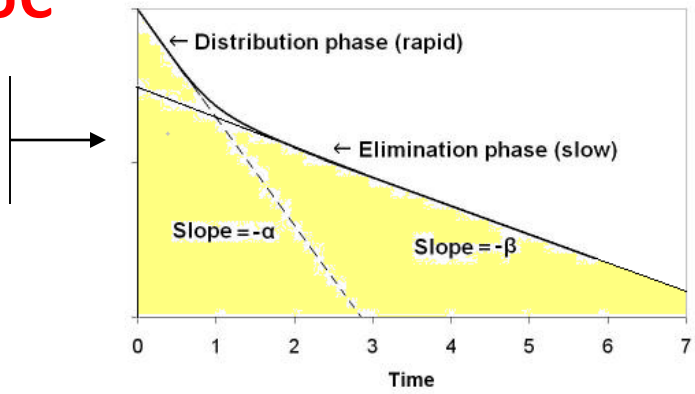
↓

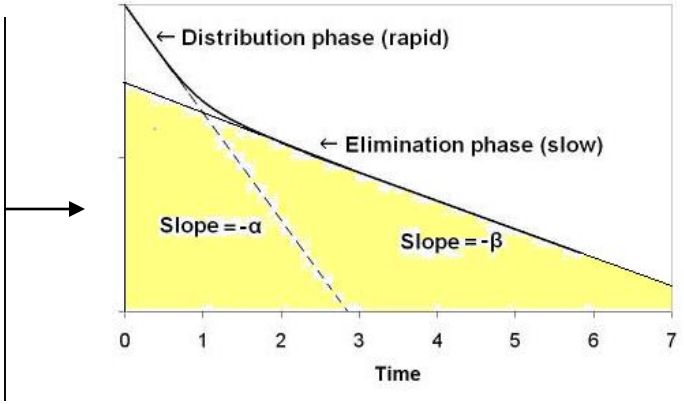
(nombreux prélèvements)

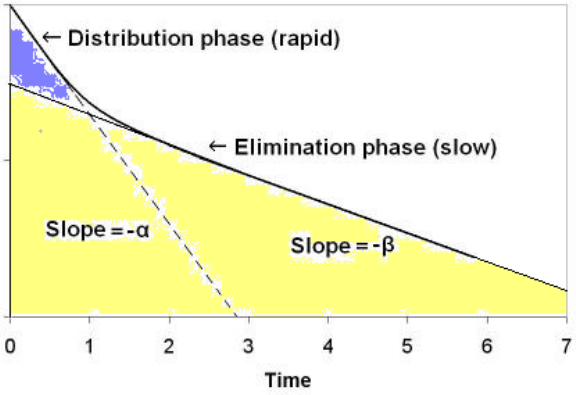
Seule la pente ß après équilibre est calculée

↓

Brochner-Mortensen correction mathématique pour la correction de la phase de distribution
= 0,990778 x C2 – 0,001218 $C2^2$







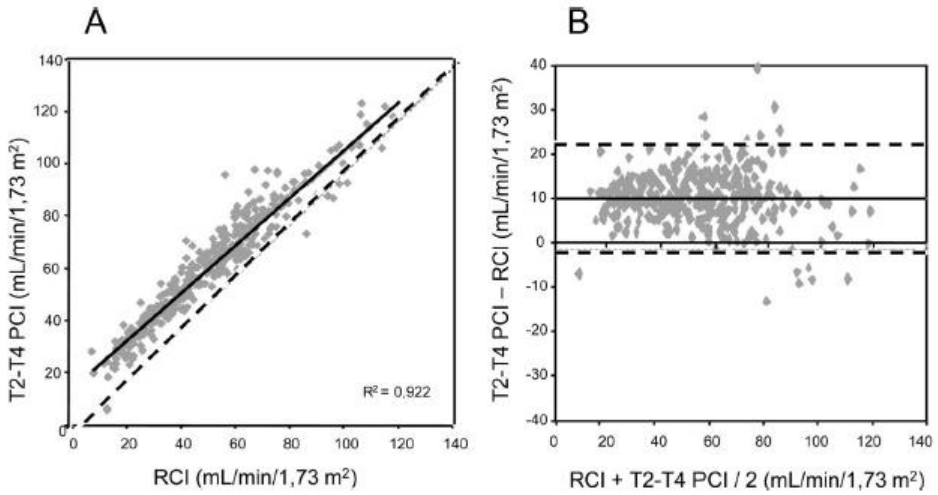
M

Clairances équivalentes?

Clairances Plasmatiques versus Urinaires

Evaluation of Sample Bias for Measuring Plasma Iohexol Clearance in Kidney Transplantation

Arnaud Stolz,[1] Guillaume Hoizey,[2] Olivier Toupance,[1] Sylvie Lavaud,[1] Fabien Vitry,[3] Jacques Chanard,[1] and Philippe Rieu[1,4,5]



	n	Bias ml/min/1.73m² (%)	Precision (SD) (ml/min/1.73m²)
T2-T4	342	+10 (+27%)	±6
T2-T6	342	+8 (+21%)	±6
T2-T24	215	+3 (+8.8%)	±5

Stolz A, Transplantation, 2010, 89, 440

Clairances Plasmatiques versus Urinaires

- Plus physiologiques
- Moins pratiques
- Différences sont systématiques

Table 4. Available procedures to perform iohexol clearance

Methodology	Indication in clinical practice	Indication in clinical research	Bibliographic examples where the procedure is described into details
Urinary clearance	Increased extracellular volume (oedema, ascites, intensive care units, etc.)	Basic (physiologic) studies Specific populations (cirrhotic, intensive care, nephrotic syndrome, oedema, etc.)	[36, 77, 125, 170]
Plasma clearance			
Multiple samples (first or fast, second or slow exponential curves and calculation of area under the curve)	High GFR values ('hyperfiltrating') subjects	Development of equations to estimate GFR Studies in hyperfiltrating patients	[52, 93, 171]
Multiple samples only for second and slow component (2 h after injection, 4 samples over 5 or 6 h, 1 sample/h) + BM correction	High precision determination (see text)	Development of equations to estimate GFR Clinical research with GFR as main endpoint	[126, 172]
Idem + late sample (8 h or 24 h)	Pre-dialysis subjects	Research in pre-dialysis subjects	[52, 77]
Simplified two or three sample method (2 samples: first at 2 or 3 h and second at 4 or 5 h) + BM correction	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint	[69, 116]
Simplified single-sample method + Jacobsson correction [110]	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint Epidemiological research	[14, 173]

Suggestions (expert opinion-based) according to the clinical or experimental context.
GFR, glomerular filtration rate; CKD, chronic kidney disease; BM, Brochner-Mortensen correction [116].

Delanaye P, Clin Kidney J, 2016, 9, 700

EKFC

Nephrol Dial Transplant (2018) 33: 1778–1785
doi: 10.1093/ndt/gfx345
Advance Access publication 8 January 2018

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

[1]Department of Nephrology, Dialysis, Transplantation, University of Liège (CHU ULg), Liège, Belgium, [2]Department of Renal Physiology, DHU-FIRE, Hôpital Bichat, AP-HP, Inserm U1149, and Paris Diderot University, Sorbonne Paris-Cité, Paris, France, [3]Néphrologie, Dialyse, Hypertension artérielle et Exploration fonctionnelle rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France, [4]Laboratory of Tissue Biology and Therapeutic Engineering, UMR 5305 CNRS, University Claude Bernard Lyon 1, Lyon, France, [5]Department of Clinical Chemistry, University of Liège (CHU ULg), Liège, Belgium, [6]Charité University Hospital, Institute of Public Health, Berlin, Germany and [7]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

Correspondence and offprint requests to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr
*These authors equally contributed as first author.
**These authors equally contributed as last senior author.

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CLINICAL RESEARCH

Comparison of Plasma Clearance With Early-Compartment Correction Equations and Urinary Clearance in High GFR Ranges

Pierre Delanaye[1,2*], Emmanuelle Vidal-Petiot[3,*], Thomas Stehlé[4,*], Laurence Dubourg[5], François Gaillard[6], Gunnar Sterner[7], Christine A. White[8], Sandrine Lemoine[5], Vincent Audard[4], Dominique Prié[9], Etienne Cavalier[10], Marie Courbebaisse[11], Hans Pottel[12] and Martin Flamant[3]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège (ULiège), Liège, Belgium; [2]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France; [3]Assitance Publique-Hopitaux de Paris (AP-HP), Department of Physiology, FHU APOLLO, Hôpital Bichat and Inserm U1149, Université de Paris, Paris, France; [4]Assistance Publique des Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Henri-Mondor, Service de Néphrologie et Transplantation, Univ Paris Est Créteil, INSERM U955, Institut Mondor de Recherche Biomédicale (IMRB), Créteil, France; [5]Néphrologie, Dialyse, Hypertension artérielle et Exploration fonctionnelle rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [6]Assitance Publique-Hopitaux de Paris (AP-HP), Hopital Bichat, Nephrology department, Université de Paris and INSERM U1149, Paris, France; [7]Department of Nephrology, Malmö University Hospital, Malmö, Sweden; [8]Department of Medicine, Queen's University, Kingston, ON, Canada; [9]Faculté de santé de l'université de Paris, hôpital Necker Enfants Malades GHU Centre-Université de Paris AP-HP, INEM INSERM U1151, Paris, France; [10]Department of Clinical Chemistry, University of Liège (ULiège), Liège, Belgium; [11]Physiology Department, Georges Pompidou European Hospital, Assistance Publique, Hôpitaux de Paris, Université de Paris, INSERM U1151-CNRS UMR8253, Paris, France; and [12]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

AJKD

Correspondence

RESEARCH LETTER

Concordance Iohexol Plasma Clearance

To the Editor:

Pierre Delanaye, MD, PhD, François Jouret, MD, PhD
Caroline Le Goff, EuSpLM, Etienne Cavalier, EuSpLM, PhD
University of Liège Hospital (ULg CHU), Liège, Belgium
Corresponding author: pierre_delanaye@yahoo.fr

Original Investigation
AJKD

Comparability of Plasma Iohexol Clearance Across Population-Based Cohorts

Bjørn O. Eriksen, Elke Schaeffner, Toralf Melsom, Natalie Ebert, Markus van der Giet, Vilmundur Gudnason, Olafur S. Indridasson, Amy B. Karger, Andrew S. Levey, Mirjam Schuchardt, Liv K. Sørensen, and Runolfur Palsson

Rationale & Objective: Glomerular filtration rate (GFR) estimation based on creatinine or cystatin C level is currently the standard method for assessing GFR in epidemiologic research and clinical trials despite several important and well-known limitations. Plasma iohexol clearance has been proposed as an inexpensive method for measuring GFR that could replace estimated GFR in many research projects. However, lack of standardization for iohexol assays and the use of different protocols such as single- and multiple-sample methods could potentially hamper comparisons across studies. We compared iohexol assays and GFR measurement protocols in 3 population-based European cohorts.

Study Design: Cross-sectional investigation.

Setting & Participants: Participants in the Age

Results: Frozen samples from the 3 studies were obtained and iohexol concentrations were remeasured in the laboratory at the University Hospital of North Norway. Lin's concordance correlation coefficient ρ was >0.96 and C_b (accuracy) was >0.99 for remeasured versus original serum iohexol concentrations in all 3 cohorts, and Passing-Bablok regression did not find differences between measurements, except for a slope of 1.025 (95% CI, 1.006-1.046) for the log-transformed AGES-Kidney measurements. The multiple-sample iohexol clearance measurements in AGES-Kidney and BIS were compared with single-sample GFRs derived from the same iohexol measurements. Mean bias for multiple-sample relative to single-sample GFRs in AGES-Kidney and BIS were −0.25 and −0.15 mL/min, and 99% and 97% of

Complete author and article information provided before references.

Correspondence to B.O. Eriksen (bjorn.odvar.eriksen@unn.no)

Am J Kidney Dis. XX(XX):1-9. Published online Month X, XXXX.

doi: 10.1053/j.ajkd.2019.10.008

KI REPORTS
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RESEARCH LETTERS

Comparison of Early-Compartment Correction Equations for GFR Measurements

Check for updates

Pierre Delanaye[1,210], Laurence Dubourg[3,10], Martin Flamant[4,10], Eric Yayo[5], Justine B. Bukabau[6], Emmanuelle Vidal-Petiot[4], Sandrine Lemoine[3], Etienne Cavalier[7,10], Elke Schaeffner[8,10], Dagui Monnet[5], Ernest K. Sumaili[6], Natalie Ebert[8,10] and Hans Pottel[9,10]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège (ULg CHU), Liège, Belgium; [2]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Caremeau, Nimes, France; [3]Néphrologie, Dialyse, Hypertension Artérielle et Exploration Fonctionnelle Rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [4]Department of Renal Physiology, DHU-FIRE, Hôpital Bichat, AP-HP, Inserm U1149, Paris, France; [5]Département de Biochimie, UFR Sciences Médicales, Université Felix Houphouët-Boigny, Abidjan, Côte d'Ivoire; [6]Renal Unit, Department of Internal Medicine, Kinshasa University Hospital, University of Kinshasa, Kinshasa, Democratic Republic of Congo; [7]Department of Clinical Chemistry, University of Liège (CHU ULg), Liège, Belgium; [8]Institute of Public Health, Charité-Universitätsmedizin Berlin, Berlin, Germany; and [9]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

KI REPORTS
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RESEARCH LETTER

Iohexol Plasma Clearance: Impact of Weighing the Syringe

Check for updates

Pierre Delanaye[1,2], Toralf Melsom[3], Etienne Cavalier[4], Hans Pottel[5], Björn O. Eriksen[3,7] and Laurence Dubourg[6,7]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège (ULiège CHU), Liège, Belgium; [2]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Nîmes, France; [3]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; [4]Department of Clinical Chemistry, University of Liège (ULiège CHU), Liège, Belgium; [5]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium; and [6]Néphrologie, Dialyse, Hypertension artérielle et Exploration fonctionnelle rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France

Correspondence: Pierre Delanaye, Service de Dialyse, CHU Sart Tilman, 4000 Liège, Belgium. E-mail: pierre_delanaye@yahoo.fr
[†]These authors equally contributed to this work
All authors are members of the European Kidney Function Consortium.

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Disponibles sur le marché…

Marqueurs	Forces	Limites
Inuline	"Gold standard" (ou historique)	Coûteux Dosage ni facile ni standardisé Impossible en clairance plasmatique Anaphylaxie

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

Disponibles sur le marché…

Marqueurs	Forces	Limites
Inuline	"Gold standard" (ou historique)	Coûteux Dosage ni facile ni standardisé Impossible en clairance plasmatique Anaphylaxie
Iothalamate	Le plus populaire aux USA Isotopique ou "froide"	Sécrétion tubulaire Allergie Iode

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
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Iohexol	Populaire en Europe Froide	Allergie Iode

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Iohexol	Populaire en Europe Froide	Allergie Iode
EDTA	Facile à mesurer	Seulement isotopique Pas disponible aux USA…et plus en Europe!!

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

Disponibles sur le marché…

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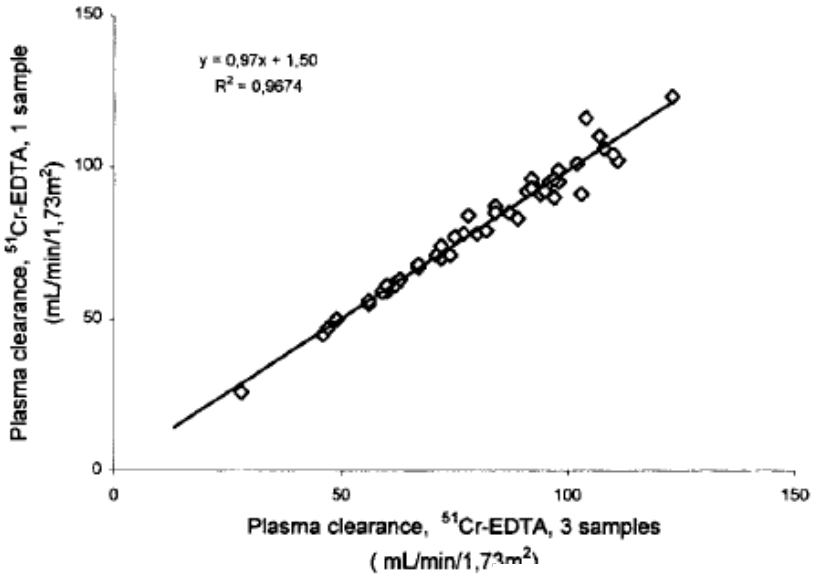
Iohexol	Populaire en Europe Froide	Allergie Iode
EDTA	Facile à mesurer	Seulement isotopique Pas disponible aux USA…et plus en Europe!!
DTPA	Facile à mesurer	Seulement isotopique Liaison aux protéines

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

Ces marqueurs sont-ils équivalents?

EDTA versus iohexol

N=49



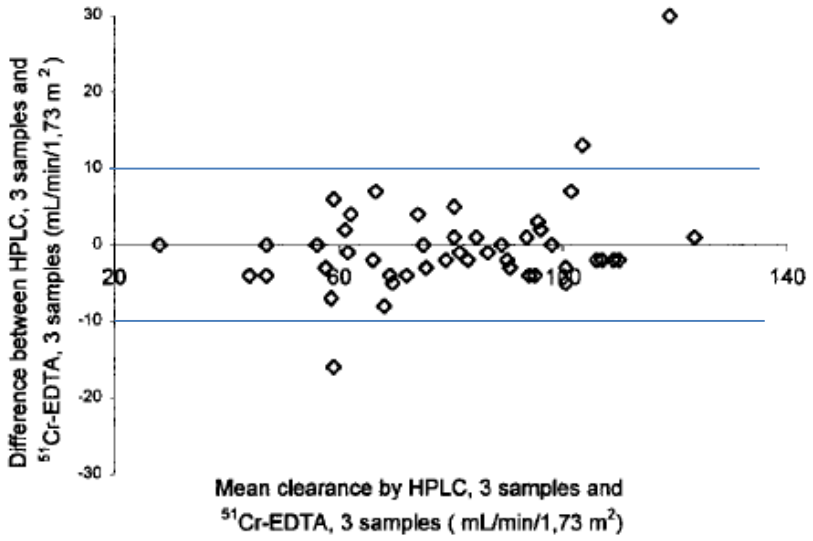


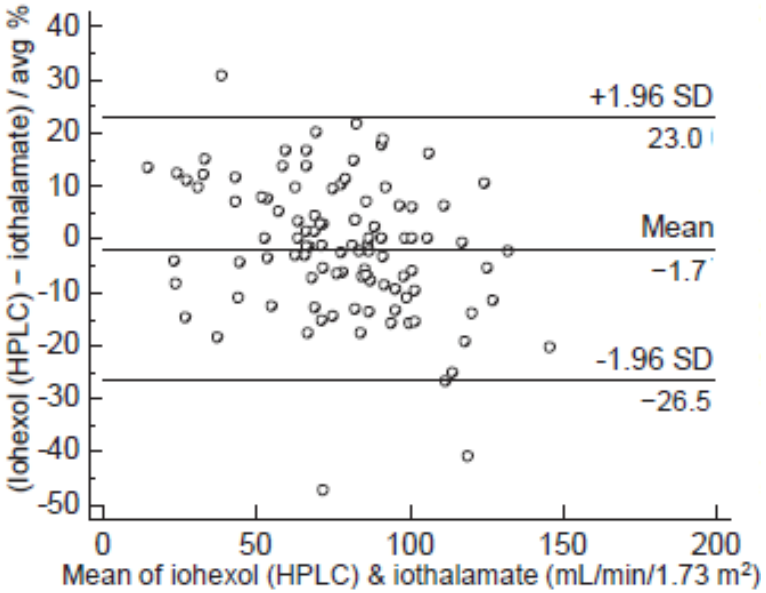
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	Clearance range (ml/min)	Difference (ml/min)	
		Mean	SD
Multiple-point clearance: 3 samples ^{51}Cr-EDTA *vs* 3 samples iohexol			
^{51}Cr-EDTA *vs* HPLC	28–134	−0.16	6.17
^{51}Cr-EDTA *vs* X-ray fluorescence	29–134	0.58	4.95
Single-point clearance: 3 samples ^{51}Cr-EDTA *vs* 1 sample			
^{51}Cr-EDTA *vs* ^{51}Cr-EDTA	26–123	−0.7	3.59
^{51}Cr-EDTA *vs* HPLC	27–125	−1.7	5.94
^{51}Cr-EDTA *vs* X-ray fluorescence	32–116	−1.32	5.78

Brandstrom E, NDT, 1998, 13, 1176

Iothalamate versus iohexol

N=102



Exactitude (concordance):
à 30%: 98%
à 15%: 80%

Delanaye, AJKD, 2016, 68, 329

AJKD
Original Investigation

Measuring GFR: A Systematic Review

*Inga Soveri, MD, PhD,[1] Ulla B. Berg, MD, PhD,[2] Jonas Björk, PhD,[3] Carl-Gustaf Elinder, MD, PhD,[4] Anders Grubb, MD, PhD,[5] Ingegerd Mejare, PhD,[6] Gunnar Sterner, MD, PhD,[7] and Sten-Erik Bäck, MSc, PhD,[5] on behalf of the SBU GFR Review Group**

Table 1. Bias and Accuracy of Index Methods Compared to Reference Method When Measuring Glomerular Filtration Rate

	No. of Pts/ Studies	Median Bias[a] (95% CI)	Mean Bias (95 % CI)	P_{30} (95% CI)	P_{10} (95% CI)	Sufficient Accuracy	Scientific Evidence	Comments[b]
Criteria for sufficient precision		≤±5%	≤±10%	≥80%	≥50%			
Index method								
DTPA								
Renal clearance	126/5	−2 (−4 to 2)	−1 (−6 to 5)	87 (81 to 93)	53 (45 to 62)	Yes	⊕⊕◯◯	Inconsistency, −1; imprecision, −1
Plasma clearance	89/2	20 (18 to 35)	13 (5 to 22)	56 (47 to 68)	19 (13 to 29)	No	⊕⊕◯◯	Study limitations −1; imprecision −1
^{51}Cr-EDTA								
Renal clearance	198/9	−5 (−7 to −3)	−2 (−8 to 4)	95 (92 to 98)	56 (50 to 64)	Yes	⊕⊕⊕◯	Imprecision, −1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Iohexol								
Renal clearance	47/2	−7 (−10 to 0)	−7 (−16 to 2)	100[c]	53 (41 to 70)	Yes	⊕⊕◯◯	Imprecision, −2
Plasma clearance	172/5	3 (0 to 6)	2 (−4 to 9)	86 (81 to 91)	50 (43 to 58)	Yes	⊕⊕⊕◯	Imprecision, −1
Iothalamate								
Renal clearance	548/13	−1 (−2 to 0)	6 (1 to 11)	97 (95 to 98)	66 (62 to 70)	Yes	⊕⊕⊕⊕	
Plasma clearance	61/1	9 (0 to 15)	11 (−6 to 29)	82 (73 to 92)	33 (23 to 47)	—	⊕◯◯◯	Study limitations, −1; imprecision, −2
Inulin								
Plasma clearance	39/2	2 (−3 to 6)	1 (−9 to 11)	100[c]	72 (59 to 87)	Yes	⊕⊕◯◯	Imprecision, −1; indirectness, −1

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage. Renal inulin clearance served as reference method. Mean bias, P_{10}, and P_{30} were estimated using generalized linear mixed models based on normal distribution (mean bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and a fixed effect for each index method ("unadjusted model results"; see Statistical Methods section). All analyses were weighed with respect to number of participants in each study. Estimates were obtained as marginal means.

Abbreviations and definitions: ⊕⊕⊕⊕, strong evidence; ⊕⊕⊕◯, moderately strong evidence; ⊕⊕◯◯, limited evidence; ⊕◯◯◯, insufficient evidence; ^{51}Cr-EDTA, chromium 51–labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; Imprecision, N < 100 in meta-analysis (−1), P_{30} lower 95% CI ≤ 80%, P_{10} lower 95% CI ≤ 50%, or median bias 95% CI ≥ ±5% (−1); Inconsistency, inconsistency in study outcomes that cannot be explained by differences in study design (−1); Indirectness, limited generalizability (−1); P_{10}, percentage of measurements by index method that differed no more than 10% from reference method; P_{30}, percentage of measurements by index method that differed no more than 30% from reference method; pts, patients; Study limitations, risk of bias due to shortcomings in individual studies (−1).

[a]Median bias was calculated directly (using the weights) for each index method together with nonparametric CIs.

[b]Strength of scientific evidence.

[c]The generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

Soveri I, Am J Kidney Dis, 2014, 64, 411

Choix du marqueur

- Seules les méthodes froides sont facilement implantables partout dans le monde
- Iohexol est disponible partout
- Très stable (labo central et/ou de “référence”)
- EQUAS (Equalis, Sweden) est disponible
- Cr-EDTA, inuline, iothalamate pas ou plus disponibles chez nous…

Iohexol au CHU de Liège

- Iohexol (clairance plasmatique), 5 mL bolus
- 5 heures
- Echantillons à 2, 3, 4 et 5 heures (+long si DFG très bas)
- Brochner-Mortensen
- 50 à 100 euros

nephron Clinical Practice

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Safety of Iohexol Administration to Measure Glomerular Filtration Rate in Different Patient Populations: A 25-Year Experience

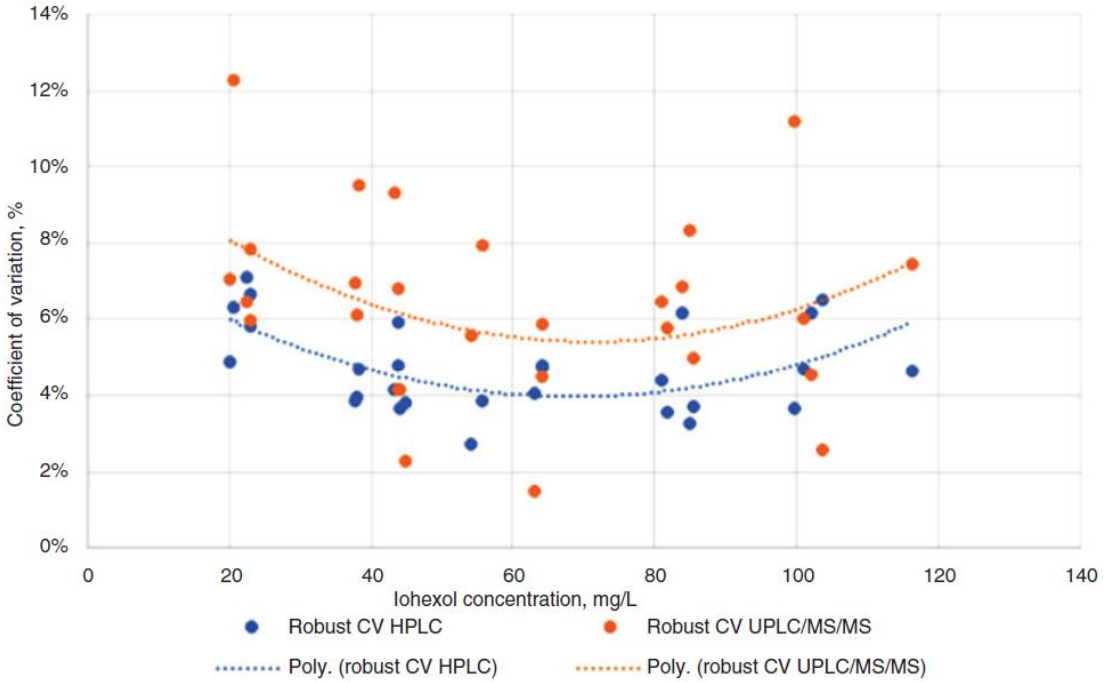
Flavio Gaspari[a] Surabhi Thakar[b] Fabiola Carrara[a] Annalisa Perna[a]
Matias Trillini[a] Maria Carolina Aparicio[a] Olimpia Diadei[a] Silvia Ferrari[a]
Antonio Cannata[a] Nadia Stucchi[a] Piero Ruggenenti[a, c] Giuseppe Remuzzi[a, c, d]
Norberto Perico[a]

[a]IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [b]Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN, USA; [c]Nephrology and Dialysis Unit, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [d]Department of Biomedical and Clinical Sciences 'L. Sacco', University of Milan, Milan, Italy

15,147 GFR measurements in 2891 patients
only one treatment-related event of moderate intensity was identified
flushing, urticaria, and itching, without sequelae after IV methylprednisolone

Gunnar Nordin, Sara Ekvall, Carolina Kristoffersson, Ann-Sofie Jonsson, Sten-Erik Bäck, Niclas Rollborn and Anders Larsson*

Accuracy of determination of the glomerular filtration marker iohexol by European laboratories as monitored by external quality assessment



4,7% for HPLC
6,4 % for mass spect

Figure 1: Mean interlaboratory CV (y-axis) vs. measured concentration of iohexol (x-axis) for laboratories using either HPLC or UPLC/MS/MS.

Nordin G, Clin Chem Lab Med, 2019, p1006

Conclusions

- Mesurer le DFG n'est pas si difficile
- Standardisation (marqueur, procédure et mesure) pourrait être encore améliorée
- Iohexol est la meilleure balance entre physiologie et faisabilité
- Iohexol est sans danger
- Iohexol est la seule chance pour une mesure du DFG standardisée dans le monde entier
- En Europe, l'iohexol va s'imposer par manque de combattants

Clinical Kidney Journal

ckj OXFORD

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CKJ Review

CKJ REVIEW

Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol?

Pierre Delanaye[1], Natalie Ebert[2], Toralf Melsom[3,4], Flavio Gaspari[5], Christophe Mariat[6], Etienne Cavalier[7], Jonas Björk[8], Anders Christensson[9], Ulf Nyman[10], Esteban Porrini[11], Giuseppe Remuzzi[12,13], Piero Ruggenenti[12,13], Elke Schaeffner[2], Inga Soveri[14], Gunnar Sterner[15], Bjørn Odvar Eriksen[3,4] and Sten-Erik Bäck[16]

[1]Department of Nephrology, Dialysis and Transplantation, University of Liège Hospital (ULg CHU), Liège, Belgium, [2]Charité University Medicine, Institute of Public Health, Berlin, Germany, [3]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway, [4]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway, [5]IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Ranica, Bergamo, Italy, [6]Department of Nephrology, Dialysis, Transplantation and Hypertension, CHU Hôpital Nord, University Jean Monnet, PRES Université de LYON, Saint-Etienne, France, [7]Department of Clinical Chemistry, University of Liège Hospital (ULg CHU), Liège, Belgium, [8]Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [9]Department of Nephrology, Skåne University Hospital, Lund, Sweden, [10]Department of Translational Medicine, Division of Medical Radiology, Skåne University Hospital, Malmö, Sweden, [11]University of La Laguna, CIBICAN-ITB, Faculty of Medicine, Hospital Universtario de Canarias, La Laguna, Tenerife, Spain, [12]Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò, Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy, [13]Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy, [14]Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [15]Department of Nephrology, Skåne University Hospital, Malmö, Sweden and [16]Department of Clinical Chemistry, Skåne University Hospital, Lund, Sweden

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Pierre Delanaye[1], Toralf Melsom[2], Natalie Ebert[3], Sten-Erik Bäck[4], Christophe Mariat[5], Etienne Cavalier[6], Jonas Björk[7], Anders Christensson[8], Ulf Nyman[9], Esteban Porrini[10], Giuseppe Remuzzi[11,12], Piero Ruggenenti[11,12], Elke Schaeffner[3], Inga Soveri[13], Gunnar Sterner[14], Bjørn Odvar Eriksen[2] and Flavio Gaspari[15]

[1]Department of Nephrology, Dialysis and Transplantation, University of Liège Hospital (ULg CHU), 4000 Liège, Belgium, [2]Metabolic and Renal Research Group, UiT The Arctic University of Norway and Section of Nephrology, University Hospital of North Norway, Tromsø, Norway, [3]Charité University Medicine, Institute of Public Health, Berlin, Germany, [4]Department of Clinical Chemistry, Skåne University Hospital, Lund, Sweden, [5]Department of Nephrology, Dialysis, Transplantation and Hypertension, CHU Hôpital Nord, University Jean Monnet, PRES Université de LYON, Saint-Etienne, France, [6]Department of Clinical Chemistry, University of Liège Hospital (ULg CHU), Liège, Belgium, [7]Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [8]Department of Nephrology, Skåne University Hospital, Lund, Sweden, [9]Department of Translational Medicine, Division of Medical Radiology, Skåne University Hospital, Malmö, Sweden, [10]University of La Laguna, CIBICAN-ITB, Faculty of Medicine, Hospital Universtario de Canarias, Tenerife, Spain, [11]Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy, [12]Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy, [13]Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [14]Department of Nephrology, Skåne University Hospital, Malmö, Sweden and [15]IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Ranica, Bergamo, Italy

European Kidney Function Consortium (EKFC)

Merci!


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