# Iohexol plasma clearance measurement protocol standardization for adults: a consensus paper of the European Kidney Function Consortium



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**International consensus supports the development of standardized protocols for measured glomerular filtration rate (mGFR) to facilitate the integration of mGFR testing in both clinical and research settings. To this end, the European Kidney Function Consortium convened an international group of experts with relevant experience in mGFR. The working group performed an extensive literature search to inform the development of recommendations for mGFR determination using 1-compartment plasma clearance models and iohexol as the exogenous filtration marker. Iohexol was selected as it is non–radio labeled, inexpensive, and safe, can be assayed at a central laboratory, and the other commonly used non–radio-labeled tracers have been (inulin) or are soon to be (iothalamate) discontinued. A plasma clearance model was selected over urine clearance as it requires no urine collection. A 1 compartment was preferred to 2 compartments as it requires fewer samples. The recommendations are based on published evidence complemented by expert opinion. The consensus paper covers practical advice for patients and health professionals, preparation, administration, and safety aspects of iohexol, laboratory analysis, blood sample collection and sampling times using both multiple and single-sample protocols, description of the mGFR mathematical calculations, as well as implementation strategies. Supplementary materials include patient and provider information sheets, standard operating procedures, a study protocol template, and support for mGFR calculation.**

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Glomerular filtration rate (GFR) is the best available index of kidney function, and international guidelines recommend wider use of measured GFR (mGFR) to assess kidney function.[1] The GFR is routinely used in patient care to diagnose chronic kidney disease (CKD), to monitor its progression, and to calculate appropriate doses of drugs that are cleared by the kidneys. As such, a simple convenient approach is needed. Equations that incorporate serum concentrations of the endogenous filtration markers, creatinine or cystatin C, are generally used to determine estimated GFR (eGFR).

Many eGFR equations have been published over the years, with each aiming to improve on past equations.[2] The most frequently used eGFR equations are based on serum creatinine, a marker that has significant non-GFR variability from muscle mass that is not adequately accounted for in eGFR equations.[3] In an attempt to overcome the shortcomings of creatinine-based estimates, various equations using an alternative endogenous marker, cystatin C alone or in combination with creatinine, have been developed.[4–7] However, cystatin C is more expensive, and eGFR based on cystatin C is also hampered by non-GFR determinants.[8] Thus, current GFR estimation using creatinine, cystatin C, or the combination can be inaccurate, particularly at the individual patient level, thereby limiting personalized care.[9]

By contrast, mGFR determination using plasma or urinary clearance of an appropriate exogenous filtration marker removes the effect of endogenous non-GFR determinants that influence the calculation of eGFR and lead to inaccuracy. However, mGFR is rarely measured in clinical practice. The original mGFR based on urinary inulin clearance was a laborious procedure that required an i.v. infusion and reliable urine collection, and although the modern methods of measuring GFR are much simpler and easier to implement, the historical reputation of being "cumbersome" still clings to mGFR.[10] Implementation strategies to facilitate mGFR uptake have also been lacking.

A variety of exogenous markers, analytical methods, and sample collection protocols for mGFR are now available, but unfortunately, the different mGFR methods often do not yield the same results.[11–13] This variability reflects (i) differences between the marker molecules; (ii) differences in clearance methods (e.g., plasma disappearance vs. urinary clearance), sampling protocols, and pharmacokinetic modeling to calculate mGFR; (iii) analytical variation between assays used to measure concentrations of the exogenous marker in blood and urine samples, which can be at low levels; and (iv) imprecision of injected volume of exogenous markers. This variability in mGFR methods is also a major obstacle for the development and validation of accurate eGFR equations as differences in eGFR performance may in fact reflect variations in mGFR rather than inaccuracy of the eGFR method itself. The need for standardization of mGFR protocols, as has been done with creatinine- and cystatin C–based assays,[14–16] is also reflected in the research recommendations of the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on evaluation and management of CKD to "harmonize and standardize existing mGFR protocols and determine their accuracy and comparability," which is the major goal of this article.[17(pS271)]

The European Kidney Function Consortium (EKFC) was established to improve the assessment of kidney function, of which GFR is a major component among others, such as tubular function. One of the goals of the EKFC is to support mGFR testing worldwide to overcome the inherent limitations associated with eGFR determination. To this end, the EKFC established an international consensus initiative to standardize mGFR testing. As a first step, the EKFC chose to focus on plasma iohexol clearance as the method for standardization, primarily for pragmatic reasons. Iohexol is safe, inexpensive, non–radio labeled, and widely available as it is used as a contrast agent to enhance computed tomography scans.[10,18] Furthermore, inulin is no longer commercially available,[19,20] and production of the alternate tracer iothalamate will soon be discontinued, narrowing the routinely available non–radio-labeled tracers to iohexol. Unlike radiolabeled tracers, iohexol is universally available, and blood samples can be frozen and then assayed at a distance from where the mGFR is performed, which greatly improves accessibility. Iohexol can be assayed from either serum or, more commonly, plasma. For simplicity's sake and to reflect more usual practice, we will refer henceforth to the method as plasma clearance.

The plasma clearance method does not require a timed urine sample collection, is not impacted by urinary retention, and can be easily performed in the outpatient setting. Plasma samples can be collected and stored frozen to be assayed at a later stage for iohexol concentrations at either a local laboratory or a more specialized external laboratory. These qualities make plasma iohexol clearance logistically feasible for widespread use in patients at clinics with limited experience and expertise in measuring GFR. Plasma iohexol clearance is already used routinely in the clinical setting in several countries, confirming that the method is generalizable.[3]

The plasma iohexol clearance method is based on pharmacokinetic models that assume 1 or 2 compartments of distribution of the exogenous marker in the human body. One-compartment slope-intercept models sample only during the elimination phase of the marker and use a correction factor to capture marker kidney elimination during the equilibration phase. Two-compartment slope-intercept models sample during both distribution and elimination phases.[18] The EKFC Consensus Paper focuses on standardizing 1-compartment clearance models as these are more commonly performed, require fewer blood samples to be collected, are less costly, and have been better validated against urinary clearance methods than 2-compartment models. There is also some evidence that results obtained using the 2 methods are similar.[21]

Thus, the EKFC convened an international group of investigators with longstanding mGFR expertise to join this International Plasma Iohexol Clearance Consensus Initiative. The

goal was to develop a standardized iohexol plasma clearance protocol for adults, excluding those who are on dialysis, such that results are more comparable across different clinical diagnostic and research settings. A second publication focusing on mGFR in children is planned. The current article does not address iohexol mGFR in non–steady states, and further research in this area is required. Investigators performed a thorough literature search, summarized the evidence, and formulated recommendations. Each section has a summary of key points, which are then more fully explored, explained, and referenced in the subsequent text. A detailed standard operating procedure document is also provided for step-by-step guidance on iohexol mGFR. All investigators reviewed and approved the final recommendations as presented here. In summary, this consensus paper gives recommendations for each step involved in iohexol clearance measurement based on published evidence complemented by expert opinion. The authors acknowledge that these recommendations were not generated using the evidence-criteria Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[22] The absence of high-quality evidence in several areas precluded this.

## INDICATIONS

### Key point

- Various bodies and experts have proposed a variety of indications for GFR measurement in both the clinical and the research realms.

Although eGFR is unbiased in the population it was developed in, it is inaccurate at the individual patient level, with both underestimation and overestimation of GFR, which becomes even more pronounced at higher levels.[23] As a result, when GFR needs to be ascertained accurately for clinical decision-making, mGFR is preferred as it is not impacted by the non-GFR determinants of serum creatinine and/or cystatin C. The 2024 KDIGO guidelines on CKD highlight clinical settings in which eGFR based on creatinine and cystatin C is insufficiently accurate and mGFR is indicated, such as "decisions about simultaneous kidney transplantation at the time of other solid organ transplantation, kidney donor candidacy, and drug dosing if there is a narrow therapeutic index or serious toxicity (e.g., chemotherapeutic agents that are cleared by the kidney)."[17(pS181)] Generally, mGFR should be considered in patients with recognized altered creatinine or cystatin C production (e.g., amputation, muscular dystrophies, liver dysfunction/cirrhosis, severe malnutrition, inflammation, and malignancy).[3] Proposed research indications include studies designed to better understand the non-GFR determinants of creatinine, cystatin C, and other potential candidate filtration markers, as well as the development of novel shorter more efficient mGFR protocols or methods, such as bedside testing.

## CONTRAINDICATIONS

### Key point

- Plasma clearance of iohexol is not recommended in patients with signs of significant volume overload, such as edema or ascites.
- Iohexol should not be administered for GFR measurement in patients with a history of severe adverse reaction to iodinated contrast media. Shellfish allergy or an allergic-like reaction to topical povidone-iodine is not a contraindication for use of iohexol for GFR measurement.

Iohexol is an iodinated contrast agent, and this has raised concerns for iodine-related allergic reactions. However, when low-dose iohexol is injected i.v. for assessment of mGFR, the risk of adverse events is low.[24–26] One study[26] retrospectively reviewed a total of 15,147 plasma iohexol clearance measurements between 1992 and 2016 in Bergamo, Italy, and identified only a single adverse event with moderately severe allergic-like symptoms. Thus, the overall rate of iohexol-related events was 0.0066%. The excellent safety profile observed is likely because of the low dose of iohexol administered for mGFR tests (5 ml), which is much lower than the doses used for imaging studies. In addition, 5 ml of iohexol for mGFR is reported to contain <1 to 2 times the daily recommended dietary intake of free iodine and, thus, is highly unlikely to saturate the thyroid.[27] Therefore, we do not recommend a washout period for patients scheduled for radioactive iodine treatment or imaging for thyroid disease, unlike what is recommended in the setting of computed tomography scans or interventional radiology, where higher doses of iohexol are used and a washout period of 3 to 6 weeks after radiocontrast administration is recommended.

The pathophysiology of adverse effects of iodinated contrast media is poorly understood, and the misconception remains that allergic-like reactions associated with iodinated contrast media are caused by hypersensitivity to iodine or shellfish. No evidence exists that iodine, an essential nutrient, can be recognized as an antigen by the immune system. Possible explanations of reactions to contrast media include non–IgE-mediated activation of mast cells and basophils, resulting in an allergic-like or pseudo-allergic reaction.[28] The American College of Radiology guidelines clarify that neither shellfish allergy nor an allergic reaction to topical povidone-iodine is considered as a risk factor for iodine allergy.[29] The Drug Allergy Guidelines by a Joint Task Force from the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology concur.[30] In particular, iodine-related shellfish allergy is a long-standing medical myth that has been debunked. The allergy to shellfish is due to tropomyosin allergy and not an allergy to iodine.[31] Seafood intolerance is also not due to its iodine content but rather to histamine-rich food, such as tuna fish, or concomitant use of drugs and alcohol that suppress histaminase.[32] Thus, an allergy to seafood, shellfish, or povidone-iodine should not be used as an exclusion factor for iohexol administration for GFR measurement. It is also not recommended that patients with a history of asthma or chronic obstructive lung disease avoid or be premedicated before receiving iodinated contrast agents.[30] There is also no evidence to support the need to stop metformin before the administration of 5 ml of iohexol.[29]

In the setting of alterations in body fluid compartments, such as significant expansion of the extracellular fluid volume, manifested by either significant peripheral edema[33] or ascites, plasma clearance methods are not recommended[13,18] because of concern of tracer sequestration into inaccessible spaces. Sequestration contributes to the plasma clearance, resulting in overestimation of the GFR. The sequestration effect has been described in small studies of patients with cirrhosis and ascites regardless of sampling strategy.[34,35] More recent findings in patients with CKD with significant pedal edema, defined as grade 3 to 4 (≥6 mm pit, lasting for >1 minute after 5-second compression over tibia or medial malleolus) confirms the overestimation associated with plasma clearance protocols.[13] In such instances, urinary clearance methods should be used. Another potential alternative for edematous subjects is continuous iohexol infusion with plasma sampling, but this needs validation before its use can be recommended.[36,37] Further research into alternative methods of measuring GFR in such circumstances are required.

The US Food and Drug Administration considers iohexol safe for pregnant women and lactating mothers[38]; however, the accuracy of iohexol plasma clearance in pregnancy is unknown. Pregnancy-related extracellular fluid volume expansion is common, and this may alter tracer distribution as seen in ascites and non–pregnancy-related edema.

## LABORATORY ANALYSIS

### Preanalytical phase: patient preparation

*Recommendations.*

- Patients who are acutely unwell should have the mGFR test rescheduled. Patients should avoid both volume depletion and overhydration as well as intermittent medications and behaviors that could transiently affect GFR before and during GFR measurement. Patients should take their scheduled medication and stay on their regular diet before the test to determine mGFR in a steady-state setting.
- Patients should wait 7 days after iodinated contrast administration for clinical purposes before undergoing an iohexol mGFR to ensure complete washout of the previously administered contrast.

Patients with acute illnesses that may transiently affect GFR (infection, nausea, vomiting, and diarrhea) should have the mGFR test rescheduled. Evidence supporting specific hydration protocols immediately before and during an mGFR test is limited, with data lacking in patients with CKD.[39] A single study of 12 healthy individuals undergoing GFR measurement via urinary inulin clearance tests 3 to 4 weeks apart found lower mGFR with high water intake (4 ml/kg every 30 minutes during the procedure) compared with low water intake (0.5 ml/kg every 30 minutes).[40] Another small study reported lower mGFR obtained using plasma clearance of $^{99m}$technicium-diethylene-triamine-pentaacetate ($^{99m}$Tc-DTPA) among patients in a fasting state compared with a low-protein pretest diet with modest oral hydration (200 ml/h water during the measurement).[39]

We recommend that for pragmatic reasons mGFR testing should be started in the morning and patients be neither dehydrated nor overhydrated when the mGFR test is performed. Thus, patients should be advised to drink water to thirst before and during the test in a pattern consistent with their usual fluid consumption. This is particularly important if delayed plasma samples are needed to accurately determine mGFR as prolonged fasting could lead to volume contraction.

To ensure that the blood does not contain iohexol at the start of the clearance measurement, the patient must not have performed any investigations with iodine-containing contrast media within 7 days. This recommendation is based on the half-life of i.v. iohexol, which is ≈2 hours in the setting of a normal GFR,[41] with adjustment for significant reductions of GFR to half-life of 14 hours and the requirement for 7 half-lives to ensure complete drug elimination (i.e., 4 days). However, as there is no information on the half-life of iohexol in advanced CKD, we are conservatively recommending a 7-day washout period. In patients with normal GFR, the washout period is likely far shorter than that but, to streamline the protocols, a 7-day period is being recommended for all.

Patients should avoid protein intake of >70 g/d (e.g., large portions of meat, fish, eggs, milk, cheese, cereals, nuts, or pulses) in the 12 hours before and during the procedure, as this can increase glomerular filtration.[42–44] Alcohol,[45] nonsteroidal anti-inflammatory drugs,[46] and strenuous exercise[47] should also be avoided before the procedure because of their propensity to cause transient changes in GFR. Although some protocols include instructions for patients to remain recumbent throughout the mGFR procedure because of the potential impact of posture on GFR,[40] evidence supporting this routine is extremely limited and its application is impractical in the ambulatory setting. As such, we do not recommend recumbency during the test unless the patient is always supine for medical reasons. In summary, iohexol injection, hemodynamic monitoring, and blood draws should preferentially be performed starting in the morning and with the patient seated and avoiding acute protein loads before or during the procedure. A template including patient preparation instructions for staff performing iohexol clearance measurement and patients undergoing the procedure is provided in the Supplementary Materials (Supplementary S1 Patient Information Sheet).

### Preanalytical phase: iohexol infusion and blood collection

*Recommendation.*

- Iohexol should be injected within a maximum of 120 seconds in the arm opposite to where the blood samples are obtained for iohexol measurement. The iohexol dose administered can be calculated by weight or volume. The exact time of injection needs to be documented, and this serves as time 0 from which the timings of subsequent blood samples are determined.

It is considered best practice to use separate i.v. cannulas, one for iohexol administration and the other, in the contralateral arm, for blood collection. In patients with severely reduced GFR, we recommend using a hand vein if possible for

the iohexol injection via a butterfly and avoiding saline lock placement in the arm designated for hemodialysis vascular access creation. If only 1 i.v. line is feasible, extensive flushing (≥30 ml of normal saline vs. the usual 5 ml when using 2 i.v. lines) is required after iohexol injection. We recommend administering iohexol, such as Omnipaque or Accupaque (GE Healthcare). Most common practice is to inject 5 ml of Omnipaque 300 (647 mg iodine/ml), corresponding to a total iohexol dose of 3235 mg. Other Omnipaque preparations are available that contain different iohexol concentrations (Table 1).[48] To standardize the iohexol administration, we recommend using 5 ml of any of the preparations with the recommended dose of iohexol used in the mGFR calculation. Iohexol doses between 1294 and 12,940 mg have yielded comparable results in a healthy population undergoing an iohexol mGFR study.[49]

It is best practice to record the syringe weight after being filled with iohexol and the needle removed. Iohexol should be injected steadily and typically within a maximum of 120 seconds. The start time of the injection is recorded as the procedure t = 0. After the injection, the i.v. cannula should be thoroughly flushed with at least 10 ml of saline. Following the injection, the empty syringe with the needle removed should be weighed again. The dose injected can be calculated gravimetrically using information in Table 1 and the following equation:

$$\text{iohexol dose (mg)} = \frac{\text{syringe weight difference (g)} * \text{iohexol concentration (mg/ml)}}{\text{iohexol solution specific gravity (g/ml)}}.$$

Alternatively, using the volume of Omnipaque delivered has been shown to be sufficiently accurate, should a scale to weigh the syringe not be available during the procedure.[50]

The timing of blood sampling depends on patient characteristics and their expected GFR level. It is important to follow appropriate sampling times to achieve optimal mGFR accuracy. Details on optimal sampling times are addressed in "Iohexol plasma clearance protocols." If there is concern that the iohexol has inadvertently been administered subcutaneously rather than i.v., the test should be stopped and repeated at a later date.[51]

Blood collection for the measurement of iohexol concentration can be performed using 5 ml ethylenediamine tetraacetic acid plasma, heparin plasma, or serum tubes. It is recommended that ∼1.5 ml of blood is drawn from the i.v. and discarded before the blood specimen collection to be used for iohexol analysis. This will prevent saline dilution of the specimen to be analyzed. After drawing blood, the line should be flushed with 5 ml normal saline. The blood tube should be inverted 3 to 5 times so that contents are well mixed. If serum tubes are being used, samples should be left at room temperature for 30 to 60 minutes to allow to clot. Specimens should then be centrifuged at between 835 and 1960 *g* for 5 to 10 minutes, after which the plasma or serum fraction should be separated and aliquoted for the iohexol assay. Because iohexol has been shown to be confined to the plasma compartment,[52] the blood should not be frozen before centrifugation, as this will cause massive cell lysis and release intracellular fluid into the plasma specimen, causing erroneous dilution of the iohexol concentration. Mild hemolysis should not significantly impact iohexol concentrations,[10] but grossly hemolyzed specimens should be discarded. Transport to the laboratory can be performed at room temperature. In case of delayed analysis (e.g., for the purposes of batch analysis), samples can be stored at –20 °C or –80 °C.

**Table 1 | Characteristics of available Omnipaque preparations**

| Omnipaque options | Iohexol, mg per ml of Omnipaque | Specific gravity at 37 °C, g/ml[a] | Iohexol, mg in 5 ml of Omnipaque |
|---|---|---|---|
| 350 | 755 | 1406 | 3775 |
| 300 | 647 | 1349 | 3235 |
| 240 | 518 | 1280 | 2594 |
| 180 | 388 | 1209 | 1940 |
| 140 | 302 | 1164 | 1510 |

[a]Omnipaque (iohexol) information sheet.[48] It can be assumed that the specific gravity is the same at 20 °C as at 37 °C (personal information from GE Healthcare).

## Iohexol analysis

***Recommendation.***

- Iohexol should be assayed in an accredited laboratory with quality control processes to monitor assay accuracy and reproducibility.

Iohexol (Chemical Abstract Services number 66108-95-0) is a nonionic, low-osmolality contrast medium with a molecular weight of 821.1 g/mol and consists of a benzene molecule with N-(2,3-dihydroxypropyl) carbamoyl groups at positions 1 and 3, iodine at positions 2, 4, and 6, and a N-(2,3-dihydroxypropyl) acetamido group at position 5. Iohexol exists as a racemic mixture of isomers referred to as endoiohexol and exoiohexol.[53] Omnipaque solutions are heat treated for sterilization purposes.[48] It has been suggested that heat sterilization of the Omnipaque solutions brings the endoiohexol and exoiohexol isomers into equilibrium.[54] This ratio needs to be taken into consideration if a laboratory prepares assay calibrators gravimetrically using iohexol powder, as the endoiohexol and exoiohexol ratios are initially different compared with the ratios in Omnipaque solutions. Thus, the laboratory would need to equilibrate the calibration material derived from iohexol powder by heat treating the solutions or leaving them at room temperature for ∼1 week if they are quantitating only endoiohexol or exoiohexol forms, but this is not relevant if the laboratory measures total iohexol (i.e., endoiohexol + exoiohexol).[55] Correct calibration of the iohexol assay is essential for the accuracy of the iohexol clearance calculation.[56] Omnipaque tends to be viscous. Thus, careful pipetting when preparing calibration material is suggested along with tight acceptance criteria (<3% difference) when changing calibration material lots. It is best practice to weigh the contrast and make stock calibration solutions gravimetrically.

It is recommended to assay iohexol at an accredited laboratory. Accuracy and reproducibility of the assay should be monitored regularly using an external quality assessment scheme from an accredited provider, such as Equalis, where weighted amounts of iohexol are added to plasma samples and distributed to laboratories participating in the external quality assessment.[57,58] However, if laboratories are unable to subscribe to such programs, they can either follow the alternatives to participation in an external quality assessment program proposed by the laboratory accreditation standard International Organization for Standardization 15189[59] or follow an alternative performance assessment plan, as suggested by the College of American Pathologists.[60] More laboratories are expected to provide such external quality assessment schemes as iohexol mGFR become more routinely performed worldwide. In the meantime, the EKFC can provide interested laboratories with lists of experienced International Organization for Standardization 15189 laboratories to help with iohexol assay validation.

Iohexol can be quantitated using techniques such as high-performance liquid chromatography ultraviolet light detection[55,61,62] or liquid chromatography–tandem mass spectrometry.[55,63,64] The iohexol assay used should have an analytical imprecision of <3%, which is less than one-half of intraindividual mGFR variation, which is ≈4.5% to 6.7%.[51,65–67] Figure 1 provides an overview of the steps involved for iohexol plasma clearance measurement. In addition, we provide a document summarizing the standard operating procedures in more detail to be used to guide through all steps of the measurement (S2. Standard Operating Procedure_Iohexol Plasma Clearance).

### Sources of error

***Recommendation.***

- Close attention should be paid to minimizing potential preanalytic and analytical errors to reduce their impact on the accuracy of the mGFR.

The iohexol mGFR is subject to both preanalytical and analytical errors. The preanalytical errors are derived from the iohexol dose administration and blood collection times, which will primarily be governed by the clinical team performing the mGFR. The analytical errors will fall on the laboratory's measurement procedure, where errors such as interference and assay calibration error could contribute to the overall GFR measurement result. It is therefore recommended that each team understands the ramifications for such errors and their contribution to the final GFR measurement result. This will assist in minimizing the error of the overall GFR measurement result.

## IOHEXOL PLASMA CLEARANCE PROTOCOLS

### Preamble

***Recommendation.***

- The blood sampling protocol for plasma iohexol clearance should be tailored for its clinical or research intent. We recommend 2 protocols: multiple-sample protocol with ≥4 samples, or a single-sample protocol. There are several factors to consider when selecting a protocol for a particular application.

Published GFR measurement protocols are heterogeneous, with varying frequency and timing of plasma sampling.[68] Most are 1-compartment multisample protocols (MSPs), with GFR calculated using a kinetic slope-intercept model and including 2 to 6 plasma samples with an initial sample obtained at 2 hours after the iohexol injection and the timing of the final sample ranging from 4 to 24 hours, depending on expected GFR. A correction factor then needs to be applied to account for the area under the curve (AUC) missing from the equilibration phase. Using >3 samples allows the visualization of the plasma iohexol concentration disappearance slope with the ability to detect and exclude obvious outlier concentrations (implausible results) for a more accurate mGFR calculation.[69] If 1 sample does not yield a result or has an erroneous result, the $R^2$ can still be calculated if >3 samples are analyzed (see "Multisample GFR calculation"). Increasing the number of plasma samples also enhances the precision of mGFR.[13] In single-sample protocols (SSPs), 1 sample is drawn after iohexol injection at a time point dependent on the expected GFR and the estimated iohexol volume of distribution.[70] The SSPs are associated with lower analytical costs, but a single-measurement iohexol plasma clearance is expected to be less precise than plasma clearance based on multiple samples, and there is no possibility for quality control based on agreement of multiple iohexol concentrations along the plasma disappearance curve.

The intraindividual coefficient of variation for mGFR by either MSP or SSP has been reported to be ≈5%.[51,65–67] In most recent studies, there are no relevant differences in coefficient of variation between SSP and MSP.[18] Intraindividual coefficient of variation includes biological variation in true GFR as well as analytical imprecision in the assays and protocols used to measure GFR. In both SSP and MSP, sample timing is the foremost consideration, and this depends on the expected GFR, as detailed below.

With a few exceptions, evidence supporting protocol specifics is hampered by the lack of simultaneous comparison to urinary clearance methods for determining mGFR. Other limitations of existing studies include small sample size, heterogeneous populations with no subgroup analysis, and the lack of measures of agreement between methods that are appropriate by today's standards. Further research comparing the 2 protocols with a reference standard urinary clearance method that does not rely on pharmacokinetic modeling assumptions is required.

Considering the available although limited evidence, we recommend selecting MSP versus SSP protocols according to the purpose of the analysis. When precision is important and the results are critical, for example, in case of kidney transplant donor and recipient eligibility, dosing of drugs with a

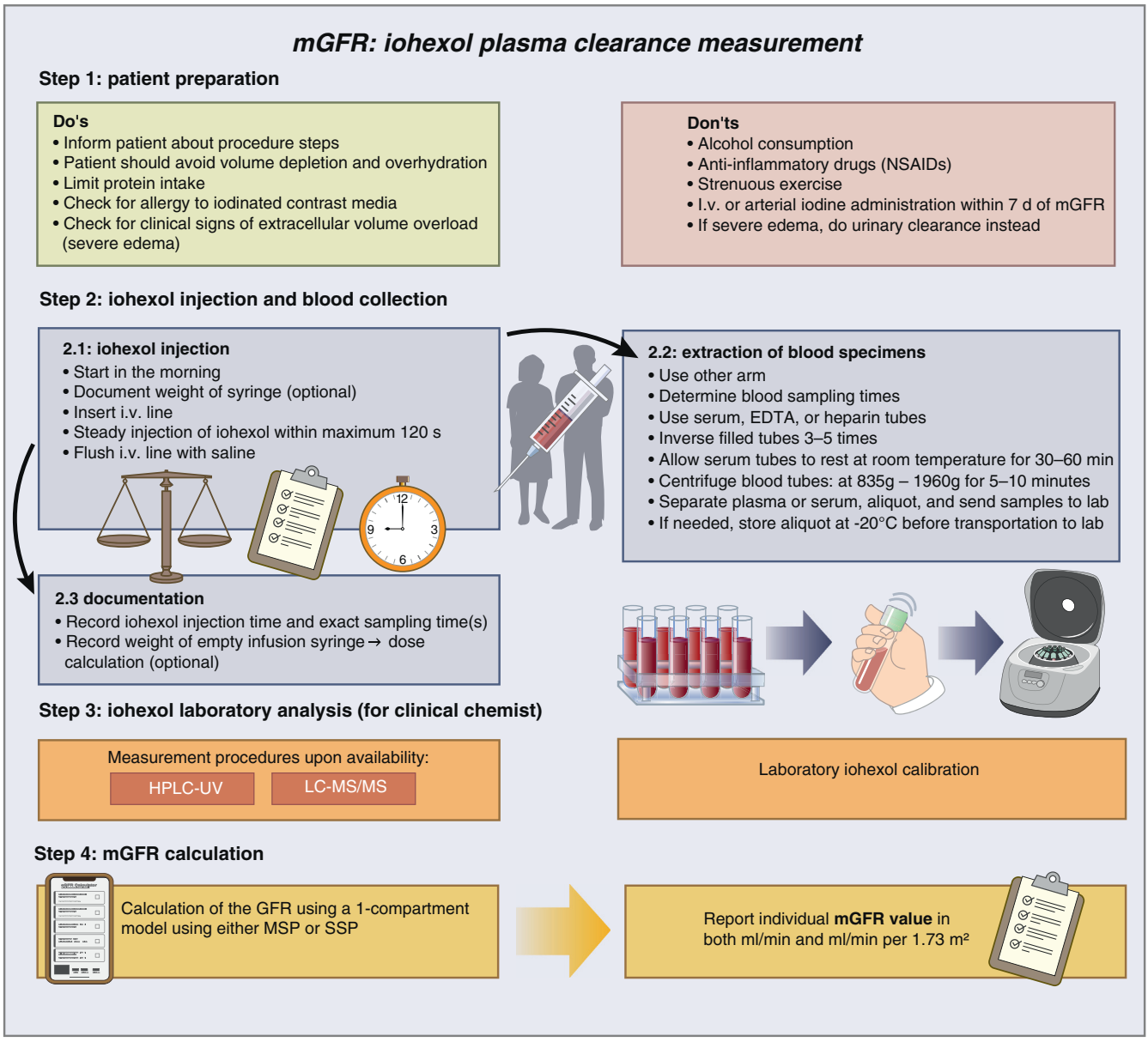


**Figure 1 | Overview of iohexol plasma clearance measurement.** The graphical overview summarizes all 4 steps required for the measurement of iohexol plasma clearance and can be used as a graphical summary to be printed out and attached to the wall in the room that the measurement takes place. EDTA, ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; HPLC-UV, high-performance liquid chromatography ultraviolet light detection; lab, laboratory; LC-MS/MS, liquid chromatography–tandem mass spectrometry; mGFR, measured glomerular filtration rate; MSP, multisample protocol; NSAID, nonsteroidal anti-inflammatory drug; SSP, single-sample protocol.

narrow therapeutic index, specific GFR eligibility cutoffs, or clinical trials where GFR is the primary exposure or outcome and feasibility allows, MSPs are recommended. At least 4 samples are recommended to ensure that at least 3 values are usable for GFR and $R^2$ calculation if a single sample is unavailable or excluded. Single-sample protocols are appropriate for investigations of large numbers of individuals, where cost must be minimized. Table 2 summarizes pros and cons for MSP and SSP.

Finally, an understudied area of importance is iohexol mGFR strategies in the setting of obesity, where tracer volume of distribution may be altered. The accuracies of single-compartment mGFRs and the performance of the various available correction factors in obesity have not been examined. One study found similar 1-compartment mGFR accuracy in patients with body surface area (BSA) $<1.98$ m$^2$ or $>1.98$ m$^2$ (the cohort median BSA) but did not provide the same analysis based on body mass index (median body mass index was 30 kg/m$^2$), suggesting that BSA does not impact protocol accuracy. No study has compared 1- and 2-compartment mGFRs in the setting of obesity. Further research is required.

**Table 2 | Pros and cons for MSPs and SSPs**

| Protocol | Pro | Con |
|---|---|---|
| MSPs | • Ability to review iohexol concentration curve, calculate coefficient of determination ($R^2$), and eliminate outliers or results that do not show good model fit | • Increased time and analytical cost |
| | • GFR result can still be calculated in event of mishap during analysis of a sample | |
| | • Protocols evaluated against gold standard renal inulin clearance at different levels of GFR | |
| SSPs | • Simple procedure; can be implemented in large investigations | • No quality control based on plausibility of individual iohexol concentrations along the plasma disappearance curve |
| | • Lower analytical cost | |

GFR, glomerular filtration rate; MSP, multisample protocol; SSP, single-sample protocol.

### Multiple-sample protocols

***Sample timing.*** *Recommendation.*

- The sampling times for MSP should be based on the expected GFR (Table 3).

Below, we outline the timing of sample collection for MSPs based on the best available evidence, while considering cost and feasibility as well as level of eGFR (Table 3). The eGFR informs when the total equilibration of iohexol in the extracellular fluid volume (ECV) is expected to occur (crucial for determining timing of initial sample), a prerequisite for use of the 1-compartment slope-intercept model as well as when iohexol concentrations are expected to be so low that analytic imprecision could significantly affect mGFR accuracy (crucial for determining timing of final sample). We provide a data intake sheet for MSP iohexol protocol in the Supplementary Material (S3. Iohexol measurement protocol).

**Table 3 | Multiple sample protocols**

| Expected patient's GFR based on eGFR | Initial and final blood sampling times after iohexol injection[a] |
|---|---|
| eGFR <30 ml/min per 1.73 $m^2$ | At 4 and 10 h with additional 1–2 hourly samples in between[b] |
| eGFR 30–59 ml/min per 1.73 $m^2$ | At 3 and 7 h with additional 1–1.5 hourly samples in between |
| eGFR >60 ml/min per 1.73 $m^2$ | At 2 and 4 h with additional 0.5–1 hourly samples in between |
| Clinical signs of excessive volume overload: edema (grades 3–4: ≥6-mm pit lasting for >1 min after 5-s compression over tibia or medial malleolus[33]) or ascites | Use urinary clearance |

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.
[a]At least 4 samples are recommended to ensure that at least 3 values are usable for GFR and $R^2$ calculation if a single sample is unavailable or excluded.
[b]If 10-hour sampling is not logistically feasible, a final sample at 8 or 24 hours is recommended. All samples should be timed to the minute of collection after injection, and these times should be used in the GFR calculation.

### Expected GFR <30 ml/min per 1.73 $m^2$

In advanced CKD, delayed final samples (10–24 hours) have traditionally been recommended for GFR measurement.[18,71] This approach is based on the finding that GFR calculated using an "early" (i.e., 5-hour) final sample is higher than GFR calculated using a "delayed" (i.e., 24-hour) final sample.[72] The overestimation caused by early final sampling has been confirmed in studies comparing plasma clearance against urinary clearance.[73] This phenomenon is thought to be due to delayed exogenous marker clearance, which results in diffusion into otherwise inaccessible compartments, leading to a delay in the attainment of the log linear elimination phase. Hence, overestimation of the renal clearance occurs when using shorter sampling protocols and a 1-compartment model.[18,71] Delaying the last sample too long, however, presents challenges with respect to patient acceptability, feasibility, and cost. Also, the results may be influenced by circadian variation in GFR.[74] An alternate approach has been explored in 1 study, in which the initial sample was extended beyond 4 hours (instead of usual 2 hours), at which time exogenous marker mixing is more complete and the plasma disappearance curve has finally reached the log-linear phase.[13] GFR measured using a 4- to 10-hour strategy was found to be more accurate (with urinary inulin clearance as the gold standard) than the 2- to 10-hour calculation, and is grounded in the physiology of marker distribution and pharmacokinetics.[13] This study did not investigate whether a 4- to 24-hour mGFR calculation is more accurate than a 4- to 10-hour calculation. Depending on the patient or test site circumstances, a 4-to 10-hour protocol might be more or less feasible/acceptable than a 4- to 24-hour protocol.

In summary, current data indicate that initial and final sampling at 4 and 10 hours with a minimum of 4 samples strikes a good balance between accuracy and feasibility. If a 10-hour final sample is not feasible, an 8-hour final sample can provide a slightly less accurate but acceptable result.[13] Alternatively, a 24-hour final sample can be used.

### Expected GFR 30 to 60 ml/min per 1.73 $m^2$

Two studies have specifically examined the midrange GFR population.[13,75] In 1 study, a 3-sample 2- to 4-hour strategy had 76% and 74% iohexol clearance-based mGFRs within 15% of the inulin clearance-based mGFR ($P_{15}$) in eGFR subgroups of 30 to 45 and 45 to 60 ml/min per 1.73 $m^2$, respectively.[75] No comparison with other sampling protocols was provided. In the other study, initial sampling at 3 hours performed similarly to a 2-hour initial sample.[13] A 7-hour final sample yielded only a slightly less accurate mGFR compared with a 10-hour final sample. In comparison, the 3-sample 2- to 4-hour protocol was more biased, less precise, and less accurate than the 3- to 7-hour protocol ($P_{30}$ of 80% vs. 88%; mean absolute error, 8.0 vs. 5.2 ml/min per 1.73 $m^2$).[13]

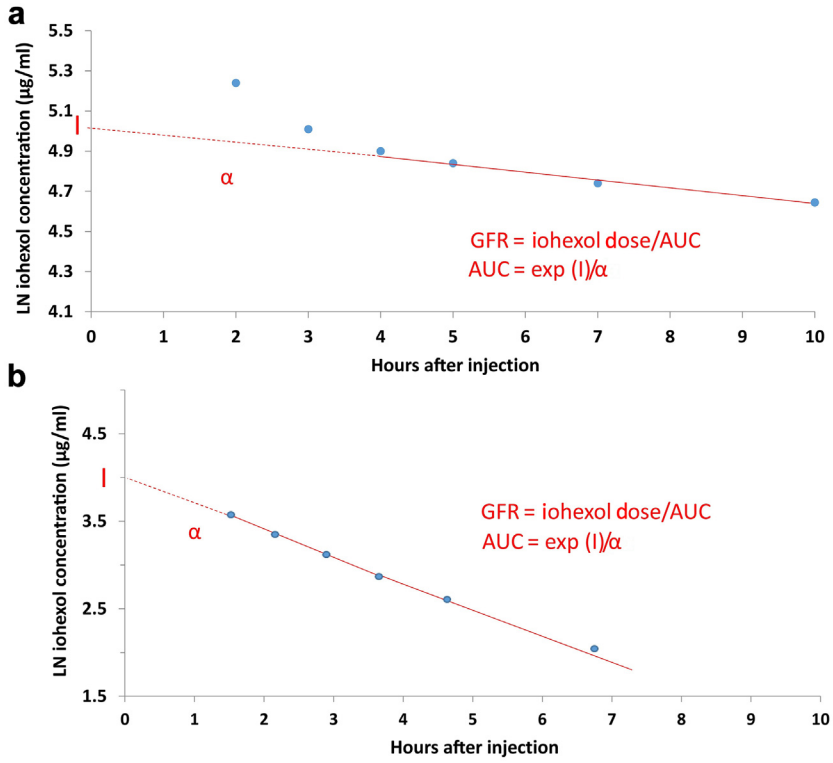


**Figure 2 | One-compartment model for multisample protocol glomerular filtration rate (GFR) determination.** *I* is the 0 time intercept, and α is the slope of the plasma iohexol elimination curve. (**a**) In this example, in a patient with GFR <30 ml/min, the terminal elimination phase is reached by 4 hours, so the regression curve is obtained using values from 4 hours onward. (**b**) In this example, in a patient with GFR >60 ml/min, the terminal elimination phase is reached by 2 hours, so the regression curve is obtained using values from 2 hours onward. AUC, area under the curve; exp, exponential function; LN, natural logarithm.

Considering all these factors and given the uncertainty of eGFR on an individual level with the potential for patients having an mGFR <30 ml/min per 1.73 $m^2$ despite eGFR >30 ml/min per 1.73 $m^2$, we recommend a 3- to 7-hour protocol with a minimum of 4 samples.

### Expected GFR >60 ml/min per 1.73 $m^2$

Three studies have compared iohexol plasma clearance and inulin urinary clearance, but all are limited by small sample size.[13,75,76] Moreover, the results were also influenced by the choice of equation used for correcting the first slope (discussed below). Delayed final sampling in subjects with high GFR results in inaccurate calculation of mGFR due to the low plasma iohexol concentration beyond 6 hours.[13] One small study in 43 young adults with type 1 diabetes and preserved GFR has shown that shorter protocols with earlier initial (60 or 90 minutes) and final (150–210 minutes) samples provided similar results to the standard 120- to 240-minute protocol. Median bias was <1 ml/min per 1.73 $m^2$, and P5 was 100% for all the shorter protocols.[77] Comparison to urinary clearance, however, was not performed.

Although further studies developing and evaluating protocols with short sampling periods are needed, especially for those with eGFR >90 ml/min per 1.73 $m^2$, the best available evidence suggests that sampling at between 2 and 4 hours with a minimum of 4 samples is optimal.

***Multisample GFR calculation.*** *Recommendation.*

- The MSP mGFR should be determined using a 1-compartment kinetic model with correction according to the Bröchner-Mortensen (BM) method before BSA indexation. Statistical software or spreadsheets can be used to calculate the mGFR. We recommend that the coefficient of determination ($R^2$) for estimating log iohexol plasma concentration over time be >0.975 and that the time concentration curve be reviewed to identify obvious outliers (implausible results) that should be excluded.

GFR is calculated using a 1-compartment kinetic model and the following equation:

$$\text{GFR} = \frac{\text{iohexol dose}}{\text{area under the plasma iohexol concentration curve } (AUC)}.$$

For the MSP recommended above, the AUC is obtained by dividing the curve's 0 time intercept by the curve's slope. The curve itself is derived by linear regression of the natural logarithms of the plasma iohexol concentrations during the sampling period (Figure 2) plotted against the time points of sample collection following iohexol injection.[78] The mGFR (ml/min) is calculated by dividing the iohexol dose by the

AUC. Intercept and slope can be determined using statistical software or a spreadsheet published as a supplement (S4. mGFR calculation using MSP_template spreadsheet; the use of this spreadsheet is the user's own responsibility. The authors cannot be responsible for any results the user generates.) The spreadsheet can be modified depending on the concentration of the iohexol preparation, the number of plasma samples, and the timing of sample collection.

At present, there are no standardized criteria for quality control of the mGFR slope derived from the declining concentration-time curve of iohexol. We recommend that the coefficient of determination ($R^2$) for plasma iohexol concentration as predicted over time be calculated for each study with at least 3 plasma samples and the GFR slope examined to identify obvious outlier points (i.e., results that are implausible) that should be excluded. If there is no obvious error/outlier, the mGFR results could be discarded if goodness of fit is judged insufficient and an $R^2 < 0.975$ has been suggested as criterion.[69] A rigorous evaluation of criteria for outlier exclusion is currently lacking in the context of mGFR calculation, and examination of this would be useful to further improve mGFR calculations.

Several different correction factors have been developed to compensate for the underestimation of the AUC using the 1-compartment model, which leads to GFR overestimation (Figure 3). The most widely used is the BM equation.[79]

$$\mathrm{mGFR_{Iohexol}(ml/min)} = 0.990778 * \mathrm{Cl_{Iohexol}} - 0.001218 * \mathrm{Cl^2_{Iohexol}}.$$

Several studies have examined the differences between the various correction factors, all of which have been shown to be small.[21,75,76,80] This is not surprising given that the slow compartment AUC contributes on average ≈90% of the total AUC.[21] Available evidence suggests that no equation performs particularly well in subjects in the high eGFR range (>120 ml/min per 1.73 $m^2$). In 1 study, poor concordance with all correction methods using urinary inulin clearance was found in the subgroup of patients with eGFR >120 ml/min per 1.73 $m^2$, although the BM and Jödal-Bröchner-Mortensen methods performed best.[76] In another study, worse performance was also observed in the highest eGFR subgroups, and the correction method of Ng-Schwartz-Munoz performed slightly better than the other equations.[75] We recommend using the BM equation because it is the most widely used and performs well overall. Further studies in patients in the high eGFR range (>120 ml/min per 1.73 $m^2$) are needed.

In the original description of the BM equation,[79] BSA indexation was applied after the BM correction. The debate about correcting for BSA before or after the BM equation is most relevant in the high eGFR range (>120 ml/min per 1.73 $m^2$) and the lower BSA ranges (e.g., for children).[81] We recommend applying the BM equation before BSA indexing and report the mGFR as both nonindexed in ml/min and indexed in ml/min per 1.73 $m^2$. The calculated BSA should also be reported. BSA is typically calculated using the Dubois and Dubois equation, although other equations do exist that better account for obesity.[82]

## Single-sample protocols

***Sample timing.*** *Recommendation.*

- The sampling time for SSP should be based on the expected GFR.

Sample collection timing for a SSP must be individualized and is calculated as follows:

$$\text{SSP sample time (min)} = \text{(ECV estimate [ml])/(expected GFR [ml/min])}.$$

This approach has been shown mathematically to minimize the effect of imprecision in the estimated distribution volume of iohexol.[70] An estimate of ECV can be calculated

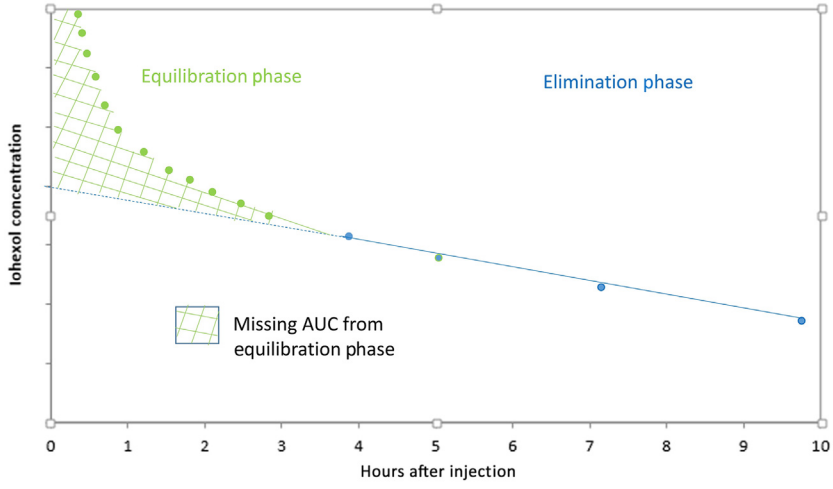


**Figure 3 | Equilibration and elimination phases of 1-compartment model.** The hatched green lines represent the area under the curve (AUC) that is not accounted for in the glomerular filtration rate (GFR) calculation, leading to GFR underestimation.

using the Granerus equations based on weight and sex (sex assigned at birth),[83,84] as shown below:

$$\text{ECV estimate}\,(\text{ml}) = (166 * \text{weight}\,[\text{kg}]) + 2490 \text{ for males, and}$$

$$\text{ECV estimate}\,(\text{ml}) = (95 * \text{weight}\,[\text{kg}]) + 6170 \text{ for females.}$$

For the expected GFR, we recommend using a validated eGFR equation as per local practice with results in ml/min per 1.73 $m^2$ reexpressed as nonbody BSA indexed GFR in ml/min.

As in MSPs, it is important in SSPs that sampling occurs once there is complete distribution of iohexol in the extracellular compartment. Conventionally, SSP studies have used a minimal sampling time of 180 minutes.[24,85–92] Calculated sampling times of <180 minutes may occur in patients with low weights and high eGFR. The limited available evidence from the seminal papers on which SSP methods were developed suggest that complete distribution and the onset of the renal iohexol elimination phase is achieved before the 180-minute mark in patients with preserved GFR.[79,93] Some evidence indicates that a single sample before 180 minutes would be acceptable,[69,94] but further research examining sample collection timing in the setting of preserved GFR is required.

***Single-sample calculation.*** *Recommendation.*

- The GFR measured with single-sample protocols should be calculated by Jacobsson equations using a numerical (iterative) method, followed by BSA indexing.

The most commonly used protocol to determine mGFR via plasma clearance derived from a single blood sample after injection of a filtration marker was developed by Jacobsson.[70] The method is based on a 1-compartment model, which incorporates the BM correction.[70,79] Jacobsson calculated GFR as an approximate solution of a set of 3 equations, but for mathematical reasons, we recommend that the equations be solved by a numerical (iterative) method.[70,92] This can be performed using statistical software or spreadsheets. Examples of coding for mGFR calculation based on SSP are available in the supplement (S5. mGFR calculation using SSP_STATA code and R code; the use of this code is the user's own responsibility. The authors cannot be taken responsible for any results the user generates.) Fleming has proposed alternative equations to those of Jacobsson's, but these have not been adequately studied with iohexol as the filtration marker.[95] The mGFR value calculated with the Jacobsson method is not indexed to the standardized BSA of 1.73 $m^2$ and should be reported as "ml/min." The value can be indexed to a BSA of 1.73 $m^2$ by multiplying by 1.73 and dividing by individual BSA, for reporting in "ml/min per 1.73 $m^2$."

Two studies have validated iohexol SSP against urinary inulin clearance in adults.[85,96] Overall, the results demonstrated good performance, but did not provide modern agreement statistics nor results at different levels of eGFR. In studies that evaluated both iohexol SSP and 1-compartment MSP in comparison with a noninulin nonurinary reference method, there is no clear evidence that MSP has a lower overall population level bias than SSP,[86,88,90,91,97] whereas there is some evidence that MSP provides better precision,[21] possibly because of reduced measurement error with a greater number of post-injection blood samples. These studies are often limited by the lack of modern agreement statistics, the absence of comparison to a reference urinary clearance method, and the use of fixed MSP and SSP protocols irrespective of level of eGFR. More studies are needed examining the performance of iohexol SSP compared with MSP at different levels of eGFR, using a urinary clearance method as a gold standard.

### Bayesian population pharmacokinetic modeling

Population pharmacokinetic modeling of iohexol and individual assessment of GFR by maximum a posteriori Bayesian estimation has been used in a few studies of kidney transplant recipients and donors, patients with liver failure, critically ill patients, and elderly patients.[98–105] Some studies have found good agreement between MSP with protocols that include full sampling in both the distribution and late elimination phases and protocols with a reduced number of samples using maximum a posteriori Bayesian estimation modeling.[99,101,102,105] No comparison of this novel approach with an independent reference method is available, and its role in relation to traditional methods in clinical practice and research is yet to be defined.

## IMPLEMENTATION OF IOHEXOL PLASMA CLEARANCE FOR GFR MEASUREMENT IN CLINICAL PRACTICE

An mGFR implementation program aims to make mGFR more widely available as a diagnostic test. Implementing mGFR in clinical practice can be facilitated by a local champion, a clinician or laboratory analyst dedicated to performing the mGFR test. The implementation of mGFR in a clinical practice can be formally evaluated using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) and PRISM (Practical, Robust Implementation and Sustainability Mode) frameworks, which would allow wider dissemination.[106–108] Depending on national requirements, the laboratory implementation requires the test facility to comply with International Organization for Standardization 15189:2022,[59] and other national standards as applicable. Requirements for implementing iohexol plasma clearance tests may include:

- allocating a designated physical site for outpatient testing, which would include basic vital sign monitoring capabilities (e.g., a preexisting "infusion clinic" or an outpatient office or a dialysis unit);
- using an electronic health record interface;
- acquiring pharmacy support for purchasing, storing, monitoring, and dispensing of iohexol for injection;
- using nursing protocols for iohexol administration and monitoring for adverse reaction, such as is routinely done for other routine infusions;
- using a phlebotomy protocol with sample processing instructions;

- ensuring compliance with regulations;
- facilitating shipping to the laboratory for plasma iohexol measurement; and
- reimbursement for procedural cost.

Costs of the mGFR test include the cost of iohexol, nursing time, phlebotomy, the iohexol assay procedure personnel and materials at the clinical laboratory, and dedicated personnel time for data review and mGFR calculation. The costs of the mGFR test are expected to vary widely based on the health care system and the site of mGFR testing. In complex health care systems with a blend of public and private payers, such as in the United States, implementation can be facilitated by using a *Current Procedural Terminology* code for mGFR and getting Medicare approval for payments.[109] Alternatively, each of the components for the mGFR test can be separately billed, similar to the billing process for i.v. infusions or stimulation tests. Sweden, where mGFR testing is routinely established in the hospital and outpatient settings, could serve as a benchmark.

## SUMMARY

International consensus supports the development of standardized mGFR protocols to facilitate the implementation of more widespread and routine mGFR testing in clinical care and research protocols. With support from the EKFC, an international group of experts performed an extensive literature search to develop recommendations for a standardized approach to determine mGFR. This consensus paper evaluated the evidence and formulated recommendations that include all aspects of iohexol plasma clearance measurement in adults not on dialysis. These recommendations include practical advice for patient preparation, preparation and administration of iohexol, blood sample collection and sampling times, laboratory analysis, mathematical calculation of mGFR, as well as aspects concerning the safety of the procedure and implementation strategies. Iohexol plasma clearance can be measured following a multisample or single-sample protocol. Iohexol plasma clearance testing is contraindicated in patients with significant edema or ascites, or with a documented severe allergy to an iodinated contrast agent. Supplementary materials are provided to assist with the mGFR calculation using either MSP or SSP. Once the infrastructure for iohexol plasma clearance measurement is established, an mGFR implementation program will facilitate the incorporation of the mGFR into both clinical practice and research protocols, including importantly future efforts to develop and validate more accurate GFR estimation equations.

## DISCLOSURE

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Supplementary material is available online at www.kidneyinternational.org.

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