Review Article

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The Evaluation of Kidney Function in Living Kidney Donor Candidates

Neetika Garg,[1] *Emilio D. Poggio*,[2] *and Didier Mandelbrot*[1]

Abstract

Living kidney donors incur a small increased risk of ESKD, of which predonation GFR is an important determinant. As a result, kidney function assessment is central to the donor candidate evaluation and selection process. This article reviews the different methods of GFR assessment, including eGFR, creatinine clearance, and measured GFR, and the current guidelines on GFR thresholds for donor acceptance. eGFR obtained using the 2009 CKD Epidemiology Collaboration equation that, although the best of estimating estimations, tends to underestimate levels and has limited accuracy, especially near-normal GFR values. In the United States, the Organ Procurement and Transplantation Network policy on living donation mandates either measured GFR or creatinine clearance as part of the evaluation. Measured GFR is considered the gold standard, although there is some variation in performance characteristics, depending on the marker and technique used. Major limitations of creatinine clearance are dependency on accuracy of timed collection, and overestimation as a result of distal tubular creatinine secretion. GFR declines with healthy aging, and most international guidelines recommend use of age-adapted selection criteria. The 2017 Kidney Disease: Improving Global Outcomes Guideline for the Evaluation and Care of Living Kidney Donors diverges from other guidelines and recommends using absolute cutoff of <60 ml/min per 1.73m^2 for exclusion and ≥90 ml/min per 1.73m^2 for acceptance, and determination of candidacy with intermediate GFR on the basis of long-term ESKD risk. However, several concerns exist for this strategy, including inappropriate acceptance of younger candidates due to underestimation of risk, and exclusion of older candidates whose kidney function is in fact appropriate for age. The role of cystatin C and other newer biomarkers, and data on the effect of predonation GFR on not just ESKD risk, but also advanced CKD risk and cardiovascular outcomes are needed.

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Introduction

Living donor kidney transplantation is the best kidney replacement therapy option for eligible patients with ESKD, offering superior outcomes compared with deceased donor transplantation (1). Recognition of its benefits to recipients and society has led to efforts to promote living donation at various levels: educating patients and health care providers, helping transplant candidates identify and approach potential donors, institution of kidney paired donation programs, acceptance of medically complex candidates, and navigating efficiency and financial barriers to donation (2–8). At the same time, ongoing success of the practice of living donation depends on ensuring the safety and good outcomes in living kidney donors, which ultimately relies on thorough evaluation and careful risk assessment before donation.

Overall Approach to Kidney Evaluation in Donor Candidates

The traditional and widely used approach to the medical component of the evaluation involves assessment of individual variables related to (*1*) current kidney health, including the GFR, proteinuria or albuminuria, and hematuria, and (2) metabolic and cardiovascular risk factors, such as hypertension, impaired glucose tolerance, obesity, and smoking, and genetic risk factors, such as family history of diabetes. GFR and proteinuria speak to the health of the kidney at the time of evaluation, which is relevant both for risk assessment of the donor candidate, and for assessment of nephron mass that will be available to the recipient via transplant. The systemic and genetic risk factors may or may not have a bearing on kidney function at the time of evaluation, but more importantly, are important to long-term donor outcomes after donation. In this context, our group conducted a national survey exploring practices on the use of different evaluation and selection strategies at transplant centers in the United States in recent years (9,10). Several criteria are sufficient for exclusion of donor candidates by themselves. For example, the survey showed that most programs exclude candidates with GFR <80 ml/min per 1.73^2, and two thirds of programs exclude hypertensive candidates requiring two or more antihypertensive drugs. Other criteria are not considered absolute contraindications, but factor into the overall decision-making

[1]Division of Nephrology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
[2]Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, Ohio

Correspondence: Neetika Garg, 1685 Highland Avenue, 4171 Medical Foundation Centennial Building, Madison, WI 53705. Email: ngarg@medicine.wisc.edu

process. For instance, the decision to exclude candidates with prediabetes is frequently multifactorial, and several programs use less strict thresholds for older candidates. One frequently cited limitation of this approach is the lack of uniformity between transplant programs, which, however, is a difficult goal given the highly nuanced nature of the process, with strong emphasis on risk-benefit discussion and informed consent.

More recently, the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Evaluation and Care of Living Kidney Donors provided a framework for acceptance of donor candidates according to their estimated postdonation risk of ESKD, in relation to the program's predetermined threshold for acceptable risk (11,12). This approach is performed through the following steps. First, ESKD risk in the absence of donation on the basis of ten demographic and health characteristics is estimated. The tool to do so was developed from a meta-analysis of seven general population cohorts (13). Several limitations of this calculator have been discussed before (14). The second step involves assessment of the postdonation risk, on the basis of the relative risk associated with the donation obtained in the study. The third and last step involves comparison of the postdonation risk estimate with the center's predefined threshold of acceptable risk. If the postdonation risk exceeds the center's threshold, the candidate is denied. If it is below the center's threshold, it accepts the candidate if they are willing to proceed after learning the risks. Strengths of this approach include the simultaneous incorporation of multiple risk factors and the uniformity it lends to the evaluation process. Major limitations include (*1*) use of cohorts with relatively short follow-up, which raise concern about underestimation of long-term risk (we do know that ESKD from diabetes and hypertension has delayed expression and increases exponentially over time [15]), and (2) important missing variables, such as family history of kidney disease, which still leave transplant providers to consider multiple additional risk factors, as they have always done. Notably, on the basis of data available in the six large cohorts in the study of healthy nondonors, the calculator uses eGFR instead of measured GFR (mGFR) or creatinine clearance (CrCl). A few other calculators are also available. A postdonation ESKD risk calculator that was developed using the United Network for Organ Sharing/Scientific Registry of Transplant Recipients database included "first-degree biologic relationship with the recipient," but did not incorporate a GFR measure, as predonation eGFR was not found to be predictive of ESKD in their exploratory models (16). This finding is counterintuitive, and contradicts previously published results from the same database where predonation eGFR was predictive of ESKD (17). Another study included donors from a single center, with up to 40 years of follow-up, and provided models for prediction of proteinuria and advanced CKD (18,19).

Importance of GFR Assessment for Donor Candidates

Regardless of the overall approach used, assessment of kidney function is crucial to the donor candidate evaluation process. Donor nephrectomy is followed by adaptive hyperfiltration to approximately 70% of predonation kidney function (20–24). If a donor goes on to develop progressive kidney disease, such as diabetic nephropathy, by virtue of having lower GFR at the time of beginning of the disease process, they would reach advanced CKD and ESKD sooner than if they had not donated a kidney, resulting in an increased risk of ESKD (25,26). Lower predonation GFR, which translates into lower postdonation GFR, has been shown to be a risk factor for ESKD in numerous studies (17,27). The study of US kidney donors between 1994 and 2016 found a hazard ratio of 0.89 for every 10 ml/min per 1.73m^2 higher eGFR value (95% CI: 0.80 to 0.99) (27). As an example, a CrCl of 85 ml/min per 1.73m^2 in a 25-year-old without any evidence of kidney disease as assessed by hematuria or proteinuria, is well below 2 SDs below mean for age for a 25-year-old (28,29), and portends a 60% (1/0.89^4) higher risk of ESKD postdonation compared with CrCl of 125 min/1.73m^2 for the same age. Additionally, ESKD is a rare event after kidney donation, but extrapolating from the above studies, it follows that the risk of advanced CKD and associated complications would be much higher in donors with lower predonation GFR (18,19).

In addition to donor safety, donor candidate GFR assessment is relevant when transplant candidates have the option of multiple donor candidates, as is often the case in kidney paired donation, or when multiple friends and family members offer to donate. The decision making is complex, because it involves HLA matching, vascular anatomy, cytomegalovirus exposure status etc., but donor kidney function is an important consideration in terms of ensuring the best recipient outcomes (30,31).

Methods of GFR Assessment

Because the knowledge of predonation GFR is a key variable factoring into decision making regarding selection of donors, this represents one of the relatively few scenarios in nephrology where accurate assessment of GFR is essential. The following methodologies are commonly used for measurement of GFR in donor candidates:

1. eGFR: several creatinine-based equations incorporate demographic and clinical variables, which serve as surrogates for the physiologic processes other than GFR that affect serum creatinine concentration, such as creatinine generation and secretion. Of the commonly used creatinine-based equations (Cockcroft-Gault, Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI), the 2009 CKD-EPI equation provides the least biased estimate at normal or mildly reduced GFR values, and has been recommended as the equation to calculate eGFR in living kidney donor candidates (32). However, as illustrated in Figure 1, it lacks accuracy, especially in subjects with close to normal GFR. $eGFR_{Cr}$ differed from mGFR by 30% or more of mGFR (a measure frequently referred to as P_{30}) in 16% of the total population and in 12% of those with eGFR of ≥60 ml/min per 1.73m^2 (32). Therefore, in a candidate with mGFR of 100 ml/min per 1.73m^2, there is a greater than one in ten chance that this equation would estimate eGFR outside the 70–130 ml/min per 1.73m^2 range. A study by Gaillard *et al.* underscored the concern that the 30% error in each direction is too wide in the context of living donor evaluation, in their retrospective study of 2733 donors. Accuracy with 10% (P_{10}) is a more relevant

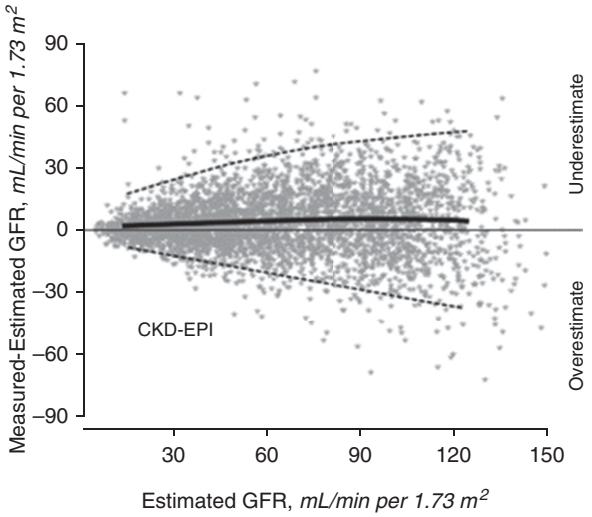

Figure 1. | Performance of the CKD-EPI creatinine-based equation in estimating mGFR (Reprinted with the permission of American College of Physicians, Inc).

performance measure, and for $eGFR_{Cr}$ was only 50% (33). In addition, $eGFR_{Cr}$ provides a slight underestimation, with median difference between mGFR and eGFR of 3.5 ml/min per 1.73m^2.

Although less affected by muscle mass and diet, cystatin C by itself is not better at predicting GFR compared with creatinine (34). The 2012 $eGFR_{Cr+CystatinC}$ equation that includes both these serum measurements fares better at estimating GFR than either alone, with only 2% of eGFRs ≥90 ml/min per 1.73m^2 differing from mGFR by >30%, but still 16% differing by >20%. Similarly, only 5% of eGFRs between 60 and 89 ml/min per 1.73m^2 differed from mGFR by >30% but 18% differed >20% (35).

Although the average biases with these estimating equations are quite low, the departures from true GFR in individual patients can be quite significant. In this context, a few recent publications on prediction of mGFR on the basis of eGFR are of interest. Huang *et al*. suggested that sufficiently high (or low), $eGFR_{Cr}$ alone, or sequential use of $eGFR_{Cr}$ followed by $eGFR_{Cr+CystatinC}$, could be used to confidently predict whether the mGFR was above (or below) thresholds commonly used for decision making (36). The pretest probability and likelihood ratios used in this study were obtained from the National Health and Nutrition Examination Survey and CKD-EPI study nondonor populations, and these computations were subsequently validated in a study of living donors from France (37). The authors found the calculator was highly sensitive in identifying all potential donors with an mGFR of <80 ml/min per 1.73m^2; however, the specificity was low at 32%. In other words, the authors and several others have concluded that if the eGFR is high enough to confidently predict an adequate mGFR, mGFR, or CrCl can be avoided, but due to low specificity, this threshold cannot be used to exclude candidates.

In addition, the use of a correction for race in the eGFR equation is highly controversial (38). Some hospitals across the United States have already removed it from the equation; however, this strategy further reduces the accuracy (39). Some others are reporting eGFR as a range, or associating the correction factor with "high muscle mass" but the performance of these strategies is untested. In an algorithm that relies on eGFR for decision making, removal of the correction factor for race from the eGFR equation could lead to inappropriate exclusion of some Black candidates (39,40).

2. mGFR: mGFR using an exogenous filtration marker is considered the gold standard for GFR assessment. Historically, inulin has been considered the perfect exogenous filtration markers because it is freely filtered in the glomerulus, and is neither secreted nor reabsorbed in the kidney. However, it is used at very few centers worldwide and is not available in the United States. Currently used methods for mGFR include chromium 51-labeled ethylenediaminetetraacetic, diethylenetriaminepentaacetic acid, iohexol, and iothalamate. The performance characteristics are generally better with renal clearance compared with plasma clearance methods. A systematic review showed that in reference to renal inulin clearance, the P_{30} values for renal clearance of all four exogenous markers were >90% (41). P_{30} of plasma chromium 51-labeled ethylenediaminetetraacetic, iohexol, and iothalamate measures are 82–86%, similar to that of $eGFR_{Cr}$ using the CKD-EPI equation (41). Due to ease of administration, plasma clearance methods are more popular than renal clearance methods; however, the accuracy is highly dependent on several factors including timing and number of samples drawn (42).

In addition to the methodologic challenges, there are very few studies documenting normal mGFR values in healthy individuals from different age groups (29,43). Data on reference ranges for mGFR using inulin for different age groups from a Baltimore study published in 1950 are summarized in Table 1 (29). Notably, this study included only 9–12 adult males in each age group. A more recent study of 141 healthy kidney donors from the Mayo Clinic showed similar results (43). Various other studies provide demographic-specific reference ranges for iothalamate-mGFR obtained from healthy kidney donor populations (44,45).

3. CrCl: given the cost, resource, and time intensiveness, and lack of availability of mGFR methods, many centers in the United States rely on timed CrCl for assessment of GFR (10,46). This is in accordance with the Organ Procurement and Transplantation Network policy on living donation which requires either mGFR or CrCl as part of evaluation of living donor candidates (47). Due to distal secretion of

Table 1. Measured GFR using inulin in healthy adult males according to age (29)

Age, Yrs	Insulin Clearance, mean±SD, ml/min per 1.73m^2
20–29	123±16
30–39	115±11
40–49	121±23
50–59	99±15
60–69	96±26
70–79	89±20
80–89	65±20

Table 2. Measured GFR, creatinine clearance, eGFR, and average of creatinine clearance and measured GFR, by age

Age, Yrs	*n*	Measured GFR, Mean±SD	Creatinine Clearance, Mean±SD	eGFR, Mean±SD	Average of Creatinine Clearance, and eGFR, Mean±SD
All	769	103±16	106±18	98±16	103±16
18–30	133	109±14	108±19	110±16	109±16
31–40	209	107±17	108±20	103±16	104±18
41–50	246	103±18	106±18	96±14	101±15
>50	181	94±15	98±16	89±15	97±17

Adapted from ref. 49 with permission.

creatinine, CrCl overestimates GFR by 10–20%, creating a positive bias. One major limitation of this method is the susceptibility to error due to inaccurate urine collections. Traditionally, the accuracy of urine collection is assessed by comparing the measured creatinine excretion rate to the expected creatinine excretion rate of 20–25 mg/kg in men and 15–20 mg/kg in women (48). This does not account for several important determinants of endogenous creatinine generation, such as age and race. Ix *et al*. developed and validated two equations that provide a more refined assessment of expected creatinine excretion rate by incorporating age, race, and serum phosphate levels (if available) in addition to sex and body weight. In one study from our group, we identified that using the equations developed by Ix *et al*., a substantially higher proportion of urine collections are accurate, including 43%, which would be deemed inaccurate, mostly under-collections, using the conventional sex- and weight-based

Table 3. Guideline recommendations for GFR assessment in living kidney donor candidates

Guideline	GFR assessment	GFR-based criteria
British Transplantation Society (2018) (52)	mGFR in everyone after initial screening using eGFR	Provides age and sex-specific GFR criteria
KDIGO (2017) (11,12)	eGFR, followed by confirmation with mGFR, CrCl or eGFR	Donor candidates with GFR ≥90 ml/min per 1.73m^2 should be considered acceptable, and those with GFR ≤60 ml/min per 1.73m^2 should be excluded Decision to approve donor candidates with GFR 60–89 ml/min per 1.73m^2 should be individualized on the basis of demographic and health profile in relation to the transplant program's acceptable risk threshold
OPTN (2021) (47)	mGFR or 24-hour CrCl	No specific recommendations provided
Canadian KPD Protocol (2015) (54)	eGFR on two separate occasions, followed by 24-hour CrCl on two separate occasions or mGFR	Provides age-specific criteria
ERBP (2013) (53)	eGFR; mGFR when more exact knowledge of GFR is needed or where is doubt regarding the accuracy of eGFR	Recommends age-dependent GFR cutoffs, such that the GFR of the remaining kidney will be >37.5 ml/min per 1.73m^2 at the time the donor reaches age 80
CARI (2010) (61)	eGFR, at least on two separate occasions or CrCl; mGFR if there is doubt regarding the accuracy or eGFR or CrCl	Recommends against accepting kidneys from donors with GFR <80ml/min per 1.73m^2
Amsterdam forum (2005) (62)	eGFR or CrCl; mGFR may be used in patients with borderline GFR determination	GFR <80 ml/min per 1.73m^2 or body-surface area-adjusted GFR <2 SD below normal on the basis of age and sex generally preclude donation Additionally noted successful transplantation from some, usually elderly living donors with GFR as low as 65–70 ml/min per 1.73m^2, indicating a need for individualization in donors with GFR <80 ml/min per 1.73m^2

mGFR, measured GFR; KDIGO, Kidney Disease: Improving Global Outcomes; CrCl, creatinine clearance; OPTN, Organ Procurement and Transplantation Network; KPD, kidney paired donation; ERBP, European Renal Best Practice, CARI, Caring for Australians and New Zealanders with Kidney Impairment.

methodology (49). Additionally, using the average of $eGFR_{Cr}$ and mGFR assessed against urinary iothalamate clearance essentially eliminated the bias in measurement; however, the accuracy as assessed by P_{10} and P_{30} measures was still modest. This study provided data on mGFR, $eGFR_{Cr}$, CrCl and average of $eGFR_{Cr}$ and CrCl from a population of otherwise healthy living donor candidates, which can serve as a reference in clinical practice (Table 2).

The available major guidelines are summarized in Table 3. Although they vary in their recommendation to use different methods, when it comes to mGFR, none provide any details on choice of exogenous marker or choice of protocol use.

GFR-based Donor Selection Criteria

GFR declines with age. Using body surface area (BSA)-adjusted GFR values 2 SD below the mean for age as a threshold under which candidates are deemed ineligible appears to be a reasonable way to ensure the actual donors have kidney function within a healthy range (50). In the example of the 25-year-old man with GFR of 85 ml/min per 1.73m^2, that is below 2 SD for age. The absence of hematuria, proteinuria, and hypertension should not necessarily be considered benign, and may be related to an unmeasured risk factor such as preterm birth, which is associated with lower nephron mass and consequent risk of CKD. These are variables not traditionally assessed during evaluation and relevant information may not be reliably available (51). A potential barrier to implementation of a strategy on the basis of 2 SD below mean for age is that most guidelines do not provide method-specific GFR cutoffs. In fact, as discussed above, there are significant differences in performance characteristics of GFR measured using exogenous filtration marker depending on the marker, methodology (plasma vs. renal clearance), and protocol used (41), and none of the major guidelines make a recommendation on the preferred technique, or provide method-specific criteria. Due to these limitations, 2 SD below mean for age, measured by any methodology, should not be considered an absolute cutoff below which donation must be excluded, but rather a way to assess whether the donor's kidney function is within the expected range for their age.

Along this line of reasoning, all major guidelines, including those from the British Transplantation Society, the European Renal Best Practice, and the Canadian Society of Transplantation, incorporate age-specific criteria (Table 3) (52–54). The one major exception is the 2017 KDIGO guideline that recommends use of fixed cutoffs of 60 ml/min per 1.73m^2 for exclusion, and of 90 ml/min per 1.73m^2 for acceptance. Between the two cutoffs, it recommends individual risk assessment on the basis of a calculator that incorporates several demographic and clinical variables, including age. These thresholds conveniently align with the GFR criteria in the KDIGO CKD classification (55). However, the disconnect from age raises concerns that young individuals with low GFR for age may be allowed to proceed to donation on the basis of their low ESKD risk estimates, which are likely to be underestimated, and that older individuals with GFR $<$90 ml/min per 1.73m^2 may be inappropriately considered suboptimal candidates for donation. An analysis of 2007 donors from France showed that one third had GFR $<$90 ml/min per 1.73m^2. As expected, donors with lower GFR were older. The lifetime renal reserve, that is, predonation GFR or expected number of remaining years of life, and the magnitude of mGFR decrease was similar in the three groups on the basis of the baseline GFR, that is, $<$80, 80–89.9, and $\geq$90 ml/min per 1.73m^2. The authors concluded the decision to accept candidates with GFR $<$90 ml/min per 1.73m^2 is closely tied to age and is reasonable for the older individuals (56). In another analysis, the same group of investigators found the use of fixed GFR criteria led to substantial misclassification of donor candidates (33,57). These discussions parallel the literature on GFR decline with healthy aging in the general population, and the suggestion to amend CKD definitions to include age-specific criteria to allow for earlier diagnosis in the young, and prevent overdiagnosis and overtreatment in the elderly (58).

Assessment of donor kidney function using BSA-adjusted and age-adapted criteria is paramount to ensuring donor safety. At the same time, assessment of absolute GFR of the transplanted kidney is important from the recipient point of view (59). A GFR of 100 ml/min per 1.73m^2 from a donor with BSA of 1.50m^2 represents an absolute GFR of 86.7 ml/min, which means approximately 43.4 ml/min will be available to the recipient after transplantation. The same GFR of 100 ml/min per 1.73m^2 from a donor with BSA of 2.00m^2 represents an absolute GFR of 115.6 ml/min, which translates into 57.6 ml/min GFR for the recipient. In the recipient context, not surprisingly, higher absolute donor GFR is associated with better kidney function after transplantation. The commonly used cutoff of 80 ml/min likely comes from an older study evaluating outcomes in the recipient (60). However, in elderly donor recipient candidates, absolute GFR$<$80 ml/min, if adequate from donor standpoint, may still yield adequate kidney function for the recipient, and better outcomes compared with dialysis.

Evaluation of each living donor candidate is highly intricate, and decision making relies heavily on education and informed consent. Assessment of kidney health is central to the evaluation process. It incorporates several variables including GFR, proteinuria, hematuria, cysts, stones, and genetics, including family history of kidney disease and ApoL1 genotype in candidates of African ancestry. This review focuses purely on the GFR assessment. mGFR using an exogenous filtration marker provides the most accurate assessment of kidney function, although variation depending on the marker and technique used certainly exists. Although the best of the creatinine-based estimating equations, the accuracy of the CKD-EPI equation alone, especially with near-normal kidney function, is suboptimal. CrCl is known to overestimate GFR, and is highly dependent on the accuracy of timed urine specimens. Average of $eGFR_{Cr}$ and CrCl, two measures of kidney function already available at most centers in the United States, improves the overall bias but accuracy is still modest. Most guidelines recommend use of criteria calibrated for age, which is consistent with our understanding of kidney function decline with healthy aging. We agree with using GFR cutoffs 2 SD below mean for age, below which donor candidates are excluded, as a reasonable measure to ensure adequate kidney function. The living donor kidney population is a unique population in which accurate assessment of kidney function is important, and in this context, the role of newer biomarkers, including but not limited to cystatin C, needs to be explored.

Additionally, long-term data on not just ESKD risk, but also CKD and cardiovascular outcomes in relation to various predonation risk factors, are also important, especially as more medically complex candidates are proceeding to donation.

Disclosures

D. Mandelbrot reports being a scientific advisor or member of CareDx and CSL Behring. E. Poggio reports having consultancy agreements with Renalytix; and reports receiving honoraria from CareDx, Novartis, and Reata. N. Garg repo rts receiving honoraria from CareDx; reports being a scientific advisor or member of BMC Nephrology Associate Editor, and the Advisory Board for CareDx.

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Author Contributions

N. Garg and D. Mandelbrot conceptualized the study; N. Garg wrote the original draft; and all authors reviewed and edited the manuscript.

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