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Age-adapted percentiles of measured glomerular filtration in healthy individuals: extrapolation to living kidney donors over 65 years

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Abstract

Objectives: Most data on glomerular filtration rate (GFR) originate from subjects <65 years old, complicating decision-making in elderly living kidney donors. In this retrospective multi-center study, we calculated percentiles of measured GFR (mGFR) in donors <65 years old and extrapolated these to donors ≥65 years old.

Methods: mGFR percentiles were calculated from a development cohort of French/Belgian living kidney donors <65 years (n=1,983), using quantiles modeled as cubic splines (two linear parts joining at 40 years). Percentiles were extrapolated and validated in an internal cohort of donors ≥65 years (n=147, France) and external cohort of donors and healthy subjects ≥65 years (n=329, Germany, Sweden, Norway, France, The Netherlands) by calculating percentages within the extrapolated 5th–95th percentile (P5–P95).

Results: Individuals in the development cohort had a higher mGFR (99.9 ± 16.4 vs. 86.4 ± 14 and 82.7 ± 15.5 mL/min/1.73 m^2)

Pierre Delanaye, François Gaillard, Hans Pottel and Marco van Londen contributed equally to this work as first or last senior authors.

PD, FG, UN, LD, NE, ES, MC, EC, CM, HP and MVL are members of the European Kidney Function Consortium.

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compared to the individuals in the validation cohorts. In the internal validation cohort, none (0%) had mGFR below the extrapolated P5, 12 (8.2%) above P95 and 135 (91.8%) between P5–P95. In the external validation cohort, five subjects had mGFR below the extrapolated P5 (1.5%), 25 above P95 (7.6%) and 299 (90.9%) between P5–P95.

Conclusions: We demonstrate that extrapolation of mGFR from younger donors is possible and might aid with decision-making in elderly donors.

Keywords: elderly; glomerular filtration rate; living kidney donors.

Introduction

Evaluation of glomerular filtration rate (GFR) is part of the screening of candidates to living kidney donation. Today, all the guidelines acknowledge that, whenever possible, the decision to authorize donation should be based on a measure of GFR with an exogenous tracer. This approach is however limited by two barriers.

First, due to the required technical expertise, data on measured GFR (mGFR) among healthy individuals are rare compared to data on GFR estimated from plasma creatinine (eGFR). Second, there is a recognized decrease in GFR with aging after 40 years. The decline in mGFR with aging has been shown on different continents and in different ethnic groups [1–10]. In fact, because most data come from living kidney donors (LKD), few data are available after 65 because few individuals donate a kidney after this age. Overall, the lack of data on mGFR combined to the "age-related" GFR decline result in very few data on mGFR available for older healthy individuals.

Yet, age at living kidney donation increased significantly over the past 10 years. In the USA more that 20% of LKD are now older than 55, while the proportion of donors younger than 40 tends to decline [11]. In France the proportion of donors older than 55 increased from 25% to 33% [12]. In Eurotransplant, the proportion of donors older than 55 increased from 37.7% to 46.4% (statistics.eurotransplant.org). For clinicians in charge of the selection of LKD, the increase in older LKD candidates is challenging: with few reference values available, there is a significant risk of misinterpreting the GFR of a given candidate. Thus, it is critical to establish reference values for older individuals.

Prospective collection of data on pre-donation mGFR in older LKD is necessary to provide correct reference values, but is a process that will take many years. As an alternative, we calculated percentiles of mGFR from a large development cohort of LKD younger than 65 years and extrapolated them to subjects older than 65 years. Additionally, we validated our results in an external validation cohort from different centers in Europe including LKD and healthy individuals from the general population older than 65 years.

Materials and methods

This is a retrospective, observational, multi-center study. The percentiles of mGFR in LKD were calculated from a French and Belgian cohort of kidney donors younger than 65 years (n=1,983), representing the development cohort. This cohort compiles data described in two previous publications [9, 13]. Briefly, in Belgium, GFR was measured by iohexol (Liège) or ^{51}Cr-EDTA (Leuven) plasma clearance [9]. In the French kidney donor study [13], GFR was measured by ^{51}Cr-EDTA plasma clearance in Paris, Bordeaux, Grenoble and Nantes, by urinary inulin clearance in Lyon, Toulouse and Clermont-Ferrand and by iohexol plasma clearance in Lyon. More details (number and timing of samples) on GFR measurements have been previously described [9, 13].

Out of the French kidney donor study [13], 147 LKD were older than 65 years, and were selected for the internal validation cohort, because they were recruited at the same centers as participants in the development cohort.

Data from six different centers were considered for the external validation cohort, either transplant centers with LKD older than 65 years or centers with healthy persons (HP) from the general population older than 65 years. HP were those without major chronic disease and no risk factor for chronic kidney disease. From Germany (Berlin), GFR was measured by iohexol plasma clearance in 18 HP from the previously described Berlin Initiative Study [14]. From France (Lyon), GFR was measured either by urinary inulin clearance (n=3) or iohexol plasma clearance (n=16), as previously described [15] in 17 HP and two LKD. From Sweden, two centers participated, one from Uppsala and one from Stockholm, where GFR was measured by iohexol plasma clearance. In Uppsala, 12 LKD were included. In Stockholm, 51 HP were included. Seventy-nine LKD from Norway were included in the current analysis [16] where GFR was measured by iohexol (n=36 plasma clearances), ^{99}Tc-DTPA (n=34, plasma clearances), and ^{51}Cr-EDTA (n=9, plasma clearances). Finally, 150 LKD were included from The Netherlands (Groningen) where GFR was measured with urinary ^{125}I-iothalamate clearances in steady-state [17]. All GFR methods used in the included cohorts are recognized reference methods [18]. All plasma clearances were multiple-sample methods. All GFR results in the current analysis were indexed for body surface area using the Du Bois equation. Importantly, LKD in our cohorts mean effective LKD, rather than donor candidates. All data were fully anonymized. The use of data was approved by the respective Ethics Committees. The local Institutional Review Boards deemed the study exempt from review.

Data are expressed as mean ± standard deviation (SD) when distribution was normal and as median with percentile 25th and 75th

when not. Normality was assessed by the Shapiro–Wilk test. Each variable was compared between cohorts by a one-way ANOVA, followed by a Holm posthoc test. Percentiles were derived from the development database, using quantiles modeled as cubic splines with two linear parts joining at one age-knot of 40 years [7, 9]. The median quantile had a constant first part (slope of zero) and a second part with a negative slope of –0.88235 mL/min/1.73 m^2 per year. For the sake of consistency, all quantiles or percentiles were adjusted to show the same shape as the medium quantile. For this purpose, we used the cubic spline root mean square error (which was 14.5) to calculate the other percentiles (Px), based on the normal approximation. The median cubic spline quantile equation was P50 = 106.2353 (–0.88235 × [age – 40] if age >40 years). All other percentiles were defined as $Px = P50 + z_x \times 14.5$, with z_x the z-score corresponding with the probability × (=area under the normal density function; in Excel z_x = NORMSINV [x]). The inverse procedure based on the normal distribution, allows to assign a percentile to each kidney donor, calculated from the actual and age-expected GFR (P50) (using 14.5 as the SD) (in Excel: NORMDIST [actual GFR, expected GFR, 14.5, true]). Above the age of 65 years, we extrapolated the percentile values using the same mathematical model. Next, we calculated the percentage of results from the internal and external validation cohorts that were within the extrapolated percentile 5th (P5) and percentile 95th (P95). Additionally, we performed a sensitivity analysis including the LKD only because it might be possible that HP are strictly not similar to LKD (who could be considered as "super-healthy").

Results

Characteristics of the development, internal and external cohorts are shown in Table 1. By protocol, individuals in the development cohort were younger than individuals in the internal or external validation cohort (47.3 ± 10.5 years vs. 68.8 ± 2.9 years or 71.4 ± 6.4 years; p<0.001). In the development cohort, individuals had a higher mGFR than individuals in the internal or external validation cohort (99.9 ± 16.4 mL/min/1.73 m^2 vs. 86.4 ± 14 mL/min/1.73 m^2 or 82.7 ± 15.5 mL/min/1.73 m^2; p<0.001). For subjects younger than 65 years, the percentiles were calculated from the development cohort database. For subjects older than 65 years, the results were extrapolated assuming the same GFR slope between 40 and 65 years and after 65 years. Data are shown in Table 2 and Figure 1. Among the 147 LKD from the internal validation cohort, none (0%) had mGFR below the extrapolated P5. Twelve (8.2%) had mGFR higher than the extrapolated P95, so 135 (91.8%) had mGFR – values between P5–P95 range (Figure 2). In the external validation cohort (n=329), five subjects had mGFR lower than the extrapolated P5 (1.5%), 25 (7.6%) had mGFR above the extrapolated P95, meaning that 299 (90.9%) had mGFR within the P5 and P95 range (Figure 3). In a sensitivity analysis, we included only the 243 LKD of the exter nal validation cohort and found similar results: 90.9% (221/243) of mGFR within the extrapolated P5 and P95 (one subject with mGFR below P5 and 21 with mGFR above the extrapolated P95) (Figure 4).

We tested whether the distribution of the percentiles (using Percentile-subgroups of 10% width) was similar for the elderly between the 147 French LKD (internal validation cohort) and the 243 LKD (external validation cohort), using a X^2 test and found no evidence for a difference between the two cohorts (p=0.23).

In a hypothetical donor candidate aged 75 years, our model would have an 'expected' GFR (corresponding to P50) of GFR = 106.2353–0.88235 × (75–40) = 75 mL/min/1.73 m^2. The P5 would be 52 mL/min/1.73 m^2. The model also allows to calculate the percentile based on the donor's

Table 1: Comparison of the development, internal and validation cohorts.

Variable	Development cohort (n=1,983)	Internal validation cohort (n=147)	External validation cohort (n=329)	p-Value
Age, years	47.3 (±10.5)	68.8 (±2.9)[a]	71.4 (±6.4)[a,b]	<0.001
Gender, n, % of women	1,212 (60.9)	91 (63.2)	187 (56.8)	0.47
Weight, kg	71.1 (±13.7)	70 (±13.8)	74.1 (±12.7)[a,b]	<0.001
Height, cm	168.1 (±8.9)	165.7 (±9.3)[a]	170 (±9.2)[a,b]	<0.001
BMI, kg/m^2	25.1 (±4)	25.3 (±3.7)	25.6 (±3.4)	0.12
BSA, m^2	1.80 (±0.20)	1.77 (±0.20)	1.85 (±0.19)[a,b]	<0.001
mGFR, mL/min/1.73 m^2	99.9 (±16.4)	86.4 (±14)[a]	82.7 (±15.5)[a,b]	<0.001
GFR tracer				<0.001
^{51}Cr-EDTA, n (%)	1,119 (56.3)	87 (60.4)	9 (2.7)	
Inulin, n (%)	294 (14.8)	47 (32.6)	3 (0.9)	
Iohexol, n (%)	576 (29.0)	10 (6.9)	133 (40.4)	
^{99m}Tc-DTPA, n (%)	0 (0.0)	0 (0.0)	34 (10.3)	
^{125}I-Iothalamate, n (%)	0 (0.0)	0 (0.0)	150 (45.6)	

[a]Significantly different from the development cohort. [b]Significantly different from the internal validation cohort. BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; mGFR, measured GFR; Cr-EDTA, chrome-ethylenediaminetetra-acetic acid; Tc-DTPA, technetium diethylenetriaminepenta-acetic acid.

Table 2: Percentiles of mGFR based on 1,983 French and Belgian living kidney donors from the development cohort (real percentiles in black and extrapolated percentiles in bold).

Age, years	P5	P10	P50	P90	P95
18	82	88	106	125	130
20	82	88	106	125	130
25	82	88	106	125	130
30	82	88	106	125	130
35	82	88	106	125	130
40	82	88	106	125	130
40	82	88	106	125	130
42	81	86	104	123	128
45	78	83	102	120	126
50	74	79	97	116	121
55	69	74	93	112	117
60	65	70	89	107	112
65	60	66	84	103	108
70	**56**	**61**	**80**	**98**	**104**
75	**52**	**57**	**75**	**94**	**99**
80	**47**	**52**	**71**	**90**	**95**
85	**43**	**48**	**67**	**85**	**90**
90	**38**	**44**	**62**	**81**	**86**
95	**34**	**39**	**58**	**76**	**82**

All values in mL/min/1.73 m^2. P, percentile; mGFR, measured GFR.

age and actual GFR. If the hypothetical 75 year old donor candidate had a GFR of 60 mL/min/1.73 m^2, then the corresponding percentile would be P15.

Discussion

In this study, we calculated percentiles of mGFR from a large cohort of effective kidney donors younger than 65 years, extrapolated them to subjects older than 65 years and tested if the mGFR fitted within the extrapolated percentiles. Our results show that more than 90% of donors and HP had mGFR within the P5 and P95 range, indicating that these GFR percentiles values can be extrapolated from younger to older donors.

By definition, LKD should represent the quintessence of healthy populations. Because several transplant programs measure GFR in candidates before kidney donation [19], several data are available in the literature describing the percentiles of mGFR in this specific population [1–10]. However, values of normal GFR above the age of 65 years are scarce [8, 10, 20], because candidates older than 65 were historically less considered as kidney donors [11, 12, 21]. The normal percentiles for mGFR were most of the time simply extrapolated from data in young LKD to older subjects. *Sensu stricto*, there was few evidence that this extrapolation is correct, or, in other words, that the slope of declining GFR observed after 40 years remains constant after 65 years. In our study, we demonstrated that these extrapolated percentiles fitted very well with real-world mGFR results. Our results confirm the decline of mGFR with aging, assuming that this decline is constant (~0.88 mL/min/1.73 m^2/years) [7–9, 22]. The extrapolated percentiles proposed in the current analysis confirm results by Eriksen et al. in the general population [8], indicating that percentiles of mGFR could help in the diagnosis of chronic kidney disease, based on an age-adapted definition [7, 8, 23, 24]. We want to emphasize the potential benefit of such percentiles in the context of kidney donation. Several guidelines recommend to consider that the lowest threshold of GFR to allow or deny donation should be adjusted to age of the donor [6, 25], a strategy that

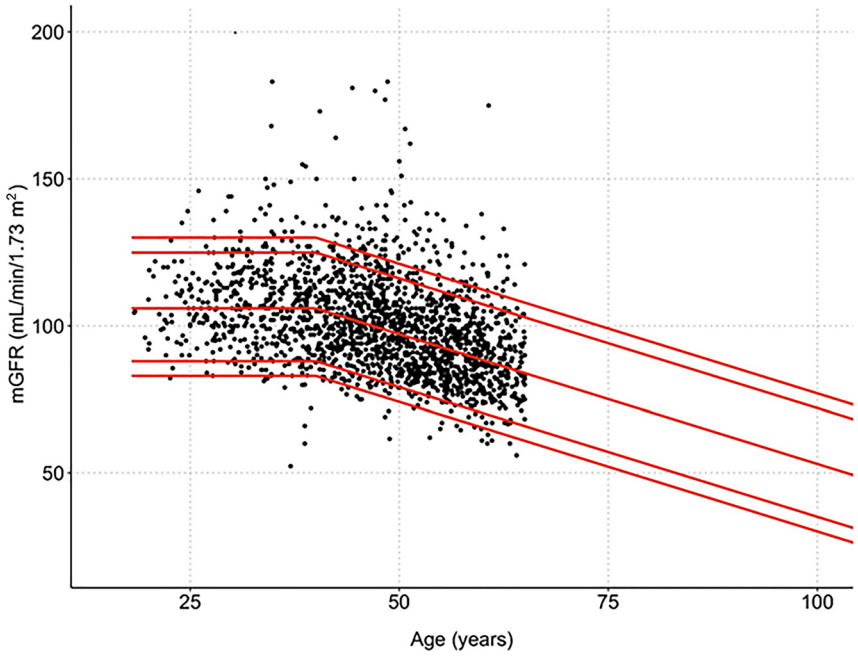

Figure 1: mGFR according to age in the development cohort (n=1,983).
Red lines are percentiles 5, 10, 50, 90 and 95, calculated from kidney donors younger than 65 years and extrapolated for ages >65 years.

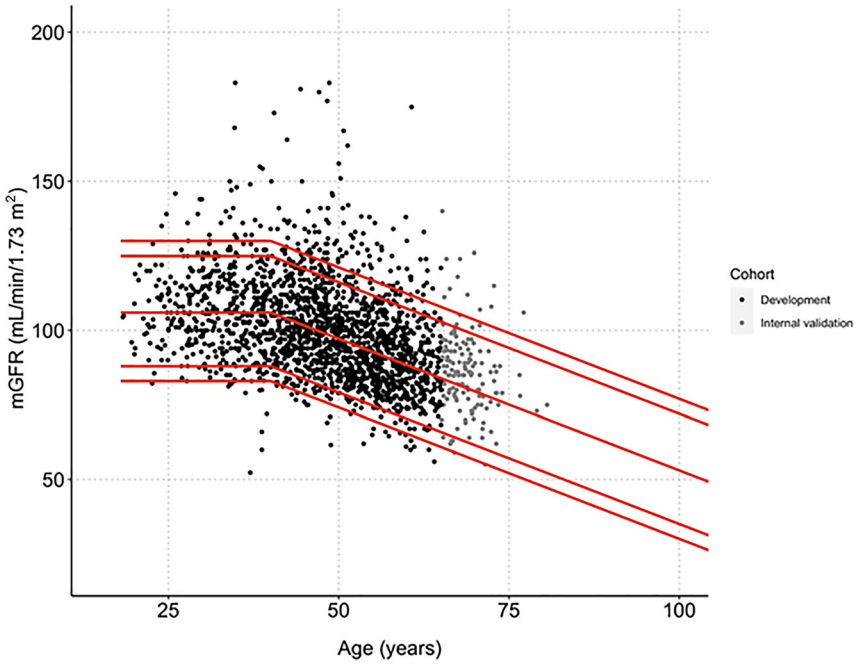

Figure 2: mGFR according to age in the development (dark dots) and internal validation cohort (n=147) (gray dots). Red lines are percentiles 5, 10, 50, 90 and 95, calculated from kidney donors younger than 65 years and extrapolated for ages >65 years.

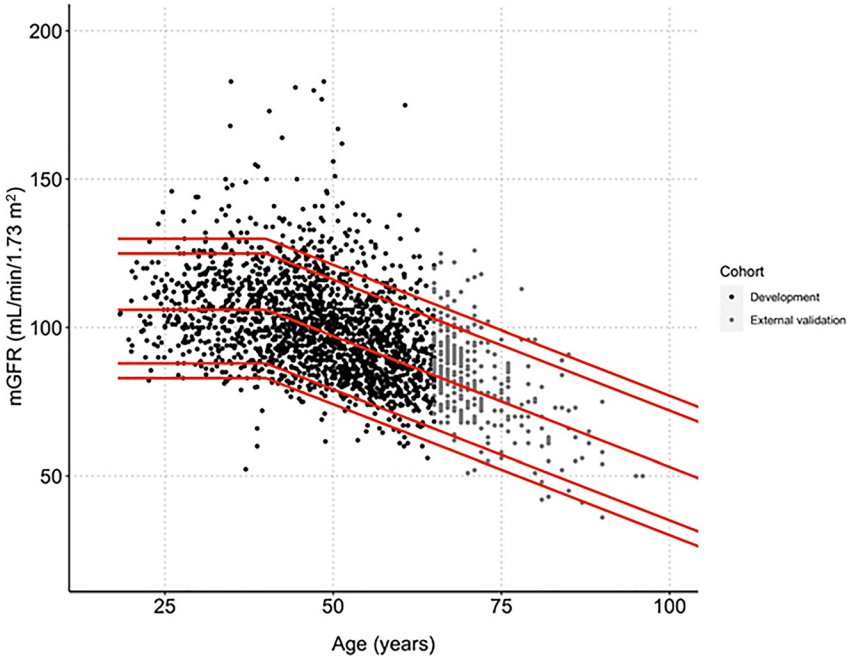

Figure 3: mGFR according to age in the development (dark dots) and external validation cohort (n=329) (gray dots). Red lines are percentiles 5, 10, 50, 90 and 95, calculated from kidney donors younger than 65 years and extrapolated for ages >65 years.

seems safe and eventually leads to a greater number of candidates [6]. The percentiles we developed could be helpful for a better interpretation of mGFR for a donor candidate older than 65 years. As an example, donation might be considered on the border between donation and refusal, based on other comorbidities and/or renal risk score [26]. Having the exact GFR percentile of a donor available might help physicians to take the right decision.

The strength of the study is the multi-center design, resulting in a fairly large cohort of aged LKD. This large database allows us to consider development, internal and external cohorts. GFR was measured by different methodologies and biomarkers (with the risk of introducing some heterogeneity), nevertheless our results seem quite consistent and the percentiles between the internal and external validation were not different. There are also

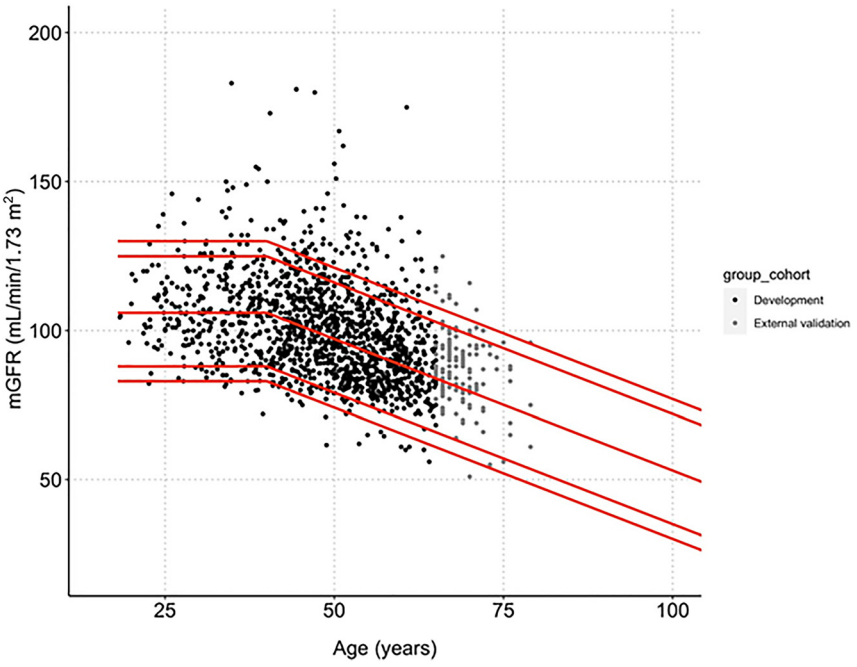

Figure 4: mGFR according to age in the development (dark dots) and external validation cohort (gray dots), considering living kidney donors only (n=243). Red lines are percentiles 5, 10, 50, 90 and 95, calculated from kidney donors younger than 65 years and extrapolated for ages >65 years.

limitations. First, as a collaborative European study, the vast majority of donors were white. Prior studies with mGFR did not suggest a difference in mGFR in black people [2, 27], but data on healthy blacks above 65 years of age are scarce [20]. Also, our results of percentiles are probably not totally transferable to other populations in Asia [3, 4]. Second, in older LKD, the individuals who are beyond the extrapolated percentiles are over the percentiles 95, not below the percentile 5. This likely is an indicator of the carefulness of physicians in interpretation of mGFR below the usual threshold considered in youngest candidates, i.e., 80 or 90 mL/min/1.73 m^2. Third, even if our sample of subjects older than 65 years was relatively large compared to the current literature, this sample did not allow us to establish percentiles over 65 years. The number of data over 75 years remains too limited to calculate correct percentiles and we could only extrapolate percentiles from younger subjects. Finally, our results are based on cross-sectional data, where ideally the decline (the slope) of GFR with aging should be established using longitudinal measurements of GFR in previous kidney donors [22, 28].

In conclusion, in a multi-center cohort of healthy subjects, we demonstrate that extrapolated percentiles of mGFR calculated in individuals younger than 65 fit well with the distribution of mGFR in individuals older than 65. Extrapolation of percentiles to individuals older than 65 might be useful in the decision of kidney donation.

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Author contributions: Conception of the study: PD, HP, FG, MVL, analysis and interpretation of data: PD, FG, JvdW, GM, IGF, LD, NE, ES, TA, KG, LC, CG, LR, MC, CM, MH, NK, EC, LW, AB, MHdB, CM, HP, MVL, Drafting of the article: PD, FG, HP, MVL. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Elke Schaeffner declared speaker honoraria for lectures from Fresenius Kabi and Siemens Healthineers. Natalie Ebert has received honoraria from Siemens Healthineers, Roche Diagnostics and Bayer AG. Other authors have nothing to declare.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Boards deemed the study exempt from review.

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