BACKGROUND

Living kidney donors are preferred for both children and adults with ESRD, showing significantly better long-term GS. The policy for accepting living donors (LDs) for children depends in part on both cultural and social conditions. Advanced age of a potential donor is regarded as a disadvantage, and many centers do not accept LDs older than 55 or 60 years for children. At our center, we have never applied an upper limit on donor age, or DRAD, but rather individually evaluated the renal function of each LD. From the beginning of
the transplantation era in 1970, grandparents have been accepted as donors on similar terms as parents.

Long-term outcome data for grandparents as donors for children with ESRD are scarce, with only a few publications. The observation time varies from two to 20 years and shows satisfactory GS. These analyses are, however, limited by a relatively low number of grandparent donors.

The aim of this retrospective survey was to evaluate our long-term strategy of allowing grandparental kidney donation on equal terms with parental donation, with a focus on long-term kidney function and GS.

2 | METHODS

Individual patient data were extracted from the NRR.

NRR is a national medical quality registry following all kidney transplant recipients from start of renal replacement therapy to death. Baseline data, for example, comorbidity, renal diagnosis, and drug treatment, are collected at time of transplantation. Follow-up data on graft loss and death are captured continuously, while a summary of all events during the year and status of the patient with regard to, for example, drug therapy, blood pressure, and clinical chemistry is updated by the last visit at the end of the year. The individual coverage is >99.9% since the start in 1969 and annual data coverage is >98%.

All first kidney, pediatric (≤18 years), LD transplantations performed in Norway in the period from 1970 to 2017 were retrieved. The NNR has national coverage and a written informed consent to perform quality and research analysis on the data obtained. Follow-up was censored in December 2018. Graft loss was defined as retransplantation or start of dialysis, including recipient death with functioning graft. Groups were compared using Kaplan-Meier analysis. The hazard ratio for graft loss for grandparent vs parent LD was calculated with Cox regression analyses adjusted for gender, donor age, recipient age, and year of transplant. In addition to this, we evaluated the risk of graft loss between pairs with a DRAD of more than 30 years vs those with an age difference of less than 30 years. The DRAD of 30 years was chosen as the average age difference between all donors and all recipients was 31 and the median was 29 years.

Kidney function at 5 (±2) years after transplantation was calculated as eGFR using the Schwartz-Lyon eGFR formula for all the recipients below 18 years of age at the time of analysis. For recipients older than 18 years, the MDRD4 formula was used.

Recipients with graft loss before the time of creatinine measurement were given a value of zero for eGFR when comparing the two groups. Statistical analyses were performed using SPSS 25. Descriptive values are given as means (SD), medians (range), and proportions (%).

3 | RESULTS

Among pediatric recipients of LD kidneys, 27 received their graft from a GPLD and 251 from a PLD. The causes of ESRD are listed in Table 1.

Demographic data of the two groups are shown in Table 2.

| TABLE 1 Primary renal disease in children transplanted 1970-2017 with first kidney tx according to donor source |
|------------------------------------------------|
| **GPLD** | **PLD** |
| CAKUT (%) | 10 (37) | 82 (33) |
| Obstructive/vesicoureteral reflux | 3 | 40 |
| Renal hypoplasia/dysplasia | 6 | 42 |
| Prune belly syndrome | 1 |
| Hereditary diseases (%) | 9 (33) | 55 (22) |
| Nephronophthisis | 2 |
| Polycystic kidney disease | 2 |
| Cystic disease, other | 2 |
| Nephropathic cystinosis | 4 |
| Primary hyperoxaluria | 1 |
| Hereditary nephropathy | 4 |
| Alport syndrome | 1 |
| Glomerulopathies and acquired diseases (%) | 8 (30) | 114 (45) |
| Glomerulonephritis | 5 |
| FSGS | 16 |
| IgA nephropathy/HSP | 1 |
| HUS | 1 |
| ANCA-associated vasculitis/arteritis | 5 |
| Amyloidosis | 3 |
| SLE | 2 |
| Interstitial nephritis | 3 |
| Drug-induced nephritis | 1 |
| Kidney tumor | 3 |
| Anti-GBM nephritis | 4 |
| Tubular/cortical necrosis | 1 |
| Nephrocalcinosis | 2 |
| Renal vascular disease due to polyanarteritis | 1 |
| Unknown | 1 |

Data on recipients with donors with an age difference of more or less than 30 years are shown in Table 3.

GPLD was significantly older than PLD, with a median age of 59 (range 42-74) years vs 41 years (23-65) (P < .001).

The median recipient age of GPLD grafts was lower than of the PLD group, 5.7 (range 1.2-18.6) vs 13.6 (range 0.8-18.9) years. The DRAD was a median of 52 (range 38-70) vs 28 (range 17-48) years for the GPLD and PLD groups, respectively.

The numbers of pre-emptive transplantations were 14/27 in the GPLD and 133/251 in the PLD, respectively.

The median follow-up time was 11.9 (range 1-46) years.

3.1 | Graft survival

Kidney transplants from GPLD had a 1-, 5-, and 10-year survival of 100%, 100%, and 90% (95% confidence interval, 85%-93%),
Kidney transplants from PLD had 1-, 5-, and 10-year survival of 93% (95% confidence interval, 89%-96%), 82% (95% confidence interval, 77%-86%), and 72% (95% confidence interval, 66%-77%), respectively. Kidney transplants from GPLD recipients and in 36 of the PLD recipients, respectively.

The reasons for graft loss were rejection (8/9) in the GPLD group. In the PLD group, the reasons for graft loss were rejection (80/129), recurrence (8/129), tumor (1/129), and other causes (4/129). Death with a functioning graft as a cause of graft loss was seen in one GPLD recipients and in 36 of the PLD recipients, respectively.

Graft survival for both groups is shown in Figure 1. Log-rank test did not show any significant difference between the groups (P = .6).

Graft loss in the total study period in the GPLD and the PLD groups was n = 9/27 (33%) and 129/251 (52%), respectively.

The reasons for graft loss were rejection (8/9) in the GPLD group. In the PLD group, the reasons for graft loss were rejection (80/129), recurrence (8/129), tumor (1/129), and other causes (4/129). Death with a functioning graft as a cause of graft loss was seen in one GPLD recipients and in 36 of the PLD recipients, respectively.

Graft loss stratified by a DRAD of more vs less than 30 years is shown in Table 5.

In univariate Cox regression analysis the hazard ratio for graft loss when dividing the groups with a DRAD > 30 years vs <30 years the results were still not significantly different (HR 0.96 (0.68, 1.35, P = .8)). In multivariate Cox regression analysis adjusted for gender, donor age, recipient age, HLA-DR mismatch, and year of transplant, this finding was similar (HR 1.09 (0.76, 1.56, P = .6)). The analysis is shown in Table 5.

### 3.2 | Kidney function

Mean eGFR estimated (±2) years after transplantation in the PLD (n = 117) and GPLD (n = 17) groups was 59.5 and 47.3 mL/min/1.73 m² (P = .028), respectively.

### 4 | DISCUSSION

In this retrospective survey with an observational time of more than 45 years, a comparable GS was shown for pediatric recipients with GPLD and PLD. This was regardless of a considerably higher median age difference between donor and recipient in the GPLD group vs the PLD group. Data were comparable when adjusting for factors such as sex, donor age, recipient age, and transplant year.
So far, three publications have addressed the subject on GPLD. Nyberg et al. published a paper in 1997 with 15 children and adolescents receiving grafts from a grandparent. The age span in the donor group was 34-70 years, with a mean age of 55 years. There were no surgical complications, and GS was 76% and 63% at 2 and 5 years, respectively. Simpson et al. published a similar paper in 2005, with a total of 13 children between 1.7 and 10.6 years old receiving grafts from grandparents with a median age of 56 (range 50-67) years. Lately, Papachristou published a paper on fourteen transplantations with grandparent donors with a follow-up time of 20 years. In this paper, patient survival was comparable with parents’ and grandparents’ donor transplants: GS was 72.1% and 57.1% after 20 years, respectively.

In comparison with these publications, our data include more grandparents and the median donor age was slightly higher. We have a median follow-up time of 11.9 years and a total follow up of almost 50 years, though data on only four donors for so long time period. The few other publications on this subject have 2, 5, 10, and 20 years of follow-up. Our data are encouraging with positive results concerning GS. The huge median age difference between donor and recipient does not seem to affect the long-term results. We could also see in the multivariate analysis that tx year had a positive impact on GS (Table 5). This may be associated with improvements in treatment and better long-term prognosis, as also seen in other cohorts.
Several issues have to be considered when evaluating a possible donor for a child, and the aim is to preserve an acceptable kidney function for a long time. The acceptance of older LD for children has been controversial. Especially for children, the main policy has been “young-for-young.” Decreased functional reserve, a higher risk for hypertension, and vascular disease have been the reason for not accepting older donors.10,11

Historically, a study of DDs showed that increased age difference between donor and recipient was associated with decreased GS.12 Later, other studies have shown similar results, even though the difference in GS has decreased.13

Due to a higher risk of vascular disease, Heidotting et al11 hypothesized that lower donor age reduces the risk for arterial hypertension and end organ damage in the recipients.

Shin et al14 analyzed the DRAD and divided the patients into four groups: ≤ -21, -20 to -1, 0-20, and ≥21 years of difference between donor and recipient. A big difference was associated with more graft rejection episodes and higher serum creatinine levels beyond the first month post-transplantation. A difference of more than 20 years was significantly correlated with worse 10-year GS. Kidneys from donors more than 55 years of age showed significantly compromised graft outcomes when transplanted into recipients younger than 30 years of age, but not in older recipients.

More data are emerging and suggest that the use of older LD has acceptable long-term outcome.15,16

A factor that can affect the function of a transplanted kidney is the size. Using an adult kidney to small children (<15-20 kg) will lead to a significant size mismatch. An early study from Bohlin and Berg looked at changes in GFR in both child recipients and adult donors. The study showed an equivalent GFR in recipient and donor adjusted for body size. These results suggest that transplantation of an adult kidney to a child results in a functional adaptation to the smaller body size of the recipient within 3 months after transplantation.17 Later, a study showed that the adult graft function did not improve with longitudinal growth as pediatric grafts did.18 Another study from Germany confirmed this, though in this study, all adult donors were DD.19 In our material, the eGFR at 5 years post-transplant was better for the PLD than for the GPLD groups. Unfortunately, we only had data from 17/27. The difference in eGFR should be interpreted cautiously due to the low number of measurements available in the GPLD group.

HLA compatibility is of importance for GS as more HLA mismatches increase the risk of rejections, even in the era of better immunosuppression.20 Poor HLA matching is also associated with enhanced sensitization making it harder to find suitable donors for repeated transplantations. We strive to select well-matched donors in order to keep HLA immunization to a minimum. In our data, we observed that parental donors had a slightly better HLA class I match with the recipients as compared to the grandparental donors, although the difference was small. The marginally better-matched parental donors could be an advantage when the patient is in need of a retransplantation.

The long-term risks linked to unilateral nephrectomy in LDs have received increased attention during the last decade. There is an increased all-cause mortality risk and risk for ESRD more than a decade after kidney donation.21,22 The total years of living with one instead of two kidneys are likely to be relevant for long-term risks after donation. In addition to this, the donor criteria are similar for older and younger donors, while most diseases occur at older age. Thus, an older donor who is healthy enough to donate is relatively healthier than a younger donor, since the medical criteria are relatively similar regardless of donor age, and has fewer remaining years living with one kidney. Consequently, selecting older donors over younger donors could have an impact on overall donor safety.23-26

From the recipient’s point of view, there is another advantage of using grandparent donors. When several potential donors are

### Table 4
Hazard ratio for graft loss comparing GPLD and PLD in Cox regression univariate and multivariate analyses

| Univariate analysis | Multivariate analysis |
|---------------------|----------------------|
| HR (95% CI)         | P-value              | HR (95% CI)         | P-value |
| GPLD vs PLD         | 0.8 (0.4, 1.6)       | .5                   | 0.98 (0.34, 2.84) | .97     |
| Male recipient      | 1.1 (0.8, 1.6)       | .6                   | 1.2 (0.8, 1.9)   | .3       |
| Donor age           | 1.0 (0.99, 1.04)     | .07                  | 1.01 (0.98, 1.04) | .6       |
| Recipient age       | 1.04 (1.01, 1.08)    | .1                   | 1.03 (1.0, 1.1)  | .2       |
| HLA-DR mm           | 1.2 (0.8, 1.7)       | .3                   | 1.5 (1.0, 2.4)   | .48      |
| Tx yr               | 0.98 (0.96, 1.99)    | .01                  | 1.0 (0.97, 1.01) | .2       |

### Table 5
Univariate and multivariate Cox regression analyses of graft loss with DRAD more than 30 vs less than 30 y

| Univariate analysis | Multivariate analysis |
|---------------------|----------------------|
| HR (95% CI)         | P-value              | HR (95% CI)         | P-value |
| Male recipient      | 1.1 (0.8, 1.6)       | .6                   | 1.07 (0.75, 1.54) | .7       |
| Age difference > 30 y | 0.96 (0.68, 1.35) | .8                   | 1.09 (0.76, 1.56) | .6       |
| HLA-DR mm           | 1.2 (0.8, 1.7)       | .3                   | 1.4 (0.9, 2.0)   | .1       |
| Tx yr               | 0.98 (0.96, 1.99)    | .01                  | 0.96 (0.94, 0.98) | <.001    |
available in a family, it is reasonable to prioritize older donors, since younger family members may donate at later time points when the first graft is failing. This allows for several LD transplants, instead of having to depend on DDs for the second or third transplant.

To our knowledge, this is the largest study on this topic, even though the number of recipients is limited. Another strength is the long and complete follow-up. There is a small overlap in donor age between the groups, but on a group level, the DRAD is substantial, and in spite of this, the results are promising.

5 | CONCLUSION

In conclusion, our strategy to use grandparents as donors has proven to be successful. We will continue to seek grandparent donors when possible. With this strategy, we can save other potential organ donors for future transplantation and at the same time reduce the overall risk for a young parent donor. With careful selection of potential donors, chronological age alone should not exclude highly motivated grandparents. With the emerging positive data on GS and long-term results, such a policy will enable centers to expand the donor pool.

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