

Preimplantation Histopathologic Assessment of Deceased Donor Kidneys

Recommendations from the Banff Time-Zero Biopsy Working Group

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Abstract

Transplantation using kidneys from deceased donors with marginal clinical characteristics is increasing to maximize access to transplant. Preimplantation biopsies of such kidneys are often obtained to determine the degree of chronic changes as an objective supplement to donor clinical-based assessment of organ quality, particularly in the United States. There is conflicting evidence and heterogeneous practice about how preimplantation biopsies should be performed, interpreted, and incorporated into organ disposition decisions. In 2022, the Banff Foundation for Allograft Pathology tasked its Time-Zero Biopsy Working Group with reviewing existing literature on preimplantation biopsies to prepare consensus recommendations on situations in which these biopsies should be performed and suggest best practices for improving reproducibility of biopsy readings. This workgroup report tabulates the Working Group's recommendations and identifies gaps that need to be filled to advance preimplantation biopsy clinical practice in donor selection. The major recommendations are that a preimplantation biopsy should be performed only when clinical assessment tools indicate that the kidney is unsuitable for utilization, that the clinical and preimplantation biopsy findings should be interpreted together for organ utilization decisions, and that digital whole slide images be promoted to facilitate setting up reporting networks of nephropathologists. Additional prospective studies using predictive modeling approaches are needed to optimize preimplantation biopsy criteria, sampling, interpretation, and incorporation into kidney allocation decisions.

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Introduction

Kidney transplantation remains the optimal treatment for kidney failure, providing the best survival, quality of life, and long-term cost.^{1–8} Because of an ongoing global organ shortage, efforts to expand transplant access have relied partly on increasing the utilization of kidneys from donors with marginal clinical characteristics. This strategy depends on reliable assessments of organ quality to determine the general suitability of a given organ for transplant and guide appropriate recipient selection. Given the limited prognostic capabilities of clinical characteristics alone—even when considered in aggregate, such as when using the kidney donor profile index (KDPI)—one commonly used supplement to clinical data is the histopathologic assessment of kidney parenchyma using preimplantation biopsies. These biopsies, also referred to as “procurement biopsies” or “allocation biopsies,” are performed during allocation to inform organ placement and

provide an objective assessment of chronic changes in the form of glomerulosclerosis (GS), interstitial fibrosis (IF), tubular atrophy (TA), arteriosclerosis, and arteriolosclerosis.

In recognition of the heterogeneity in preimplantation biopsy practices and conflicting literature on their value in kidney allocation, the Banff Foundation for Allograft Pathology tasked its Banff Time Zero Biopsy Working Group to develop consensus recommendations on situations in which preimplantation kidney biopsies should be performed and on best practices for improving preimplantation biopsy reproducibility. To fulfill these objectives, Working Group members reviewed preimplantation biopsy literature, focusing on evidence regarding (1) situations in which preimplantation biopsies facilitate organ allocation; (2) optimal methods of tissue sampling, processing, and interpretation; and (3) specific thresholds of chronic changes (if any) that should be used to support organ disposition decisions. Recommendations regarding

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each of these topics were compiled by Working Group members after appraisal of existing evidence, and the quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.^{1–6} During the course of literature review, Working Group members noted a paucity of high-quality evidence on each of the listed domains. As a result, the Working Group additionally focused on identifying specific knowledge gaps that needed to be addressed in future research to inform the development of biopsy best practices. This article discusses the Working Group's recommendations and outlines the key evidence used to prepare these recommendations.

Choosing Which Organs Should Undergo Preimplantation Histopathologic Assessment

In the United States, most deceased donor kidneys recovered for transplant undergo a preimplantation biopsy, although there is practice pattern variation between organ procurement organizations (OPOs) whereby biopsy use ranges from 23% to 78% of kidneys.⁹ This heterogeneity is starkest among higher-quality kidneys, whereas lower-quality kidneys are almost always biopsied across all OPOs.⁹ The decision to perform a biopsy is typically shared by both the OPO and the accepting transplant center, which each may have their own prespecified donor criteria to trigger preimplantation histologic assessment.^{10,11} These criteria most commonly include characteristics such as donor age (used as a criteria for biopsy by 53% of OPOs and 65% of centers), history of hypertension (63% and 48%, respectively) or diabetes (60% and 51%, respectively), donation after cardiac death (53% and 43%, respectively), AKI (40% and 56%, respectively), or elevated serum creatinine (60% and 42%, respectively).^{10,11} As of 2023, the US Organ Procurement and Transplantation Network requires that OPOs perform preimplantation biopsies on kidneys from adult deceased donors with any of the following criteria: older than 60 years; age 50–59 years with hypertension, death from stroke, or final creatinine ≥ 1.5 mg/dl; urine output < 100 ml in 24 hours; KRT; diabetes; or KDPI $> 85\%$.¹² Notably, inflations of KDPI values may occur in instances of reversible elevations of creatinine or very recent onset diabetes or hypertension.

Non-US data on preimplantation biopsy practices are less readily available, except in circumstances in which such biopsies are not typically used, such as Eurotransplant, Belgium, and France. In the United Kingdom, routine preimplantation biopsies are predominantly performed by a single center (Cambridge) on expanded criteria donor (ECD) kidneys declined by other centers. An Australia and New Zealand Dialysis and Transplant Registry analysis of outcomes of kidneys from donors with AKI found that only 15% of transplanted kidneys had a preimplantation biopsy, including 28% from donors with AKI.¹³ The differences in US and European biopsy practices are likely multifactorial, including risk aversion at US centers related to a punitive regulatory structure, differences in underlying donor pools, and the fact that post-transplant outcomes in the United States are better within 1 year but worse after 1 year compared with the United Kingdom or Australia/New Zealand.¹⁴

Efforts to eliminate the use of preimplantation kidney biopsies are rooted in the criticism that performing preimplantation biopsies increases the risk of kidney nonutilization, based predominantly on US data showing biopsy results are commonly listed as a rationale for organ nonuse, and an association between performing a biopsy and nonuse in retrospective registry studies.^{9,15–17} However, assuming a causal relationship from these studies presupposes that kidneys discarded based on biopsy results would otherwise have been transplanted. By contrast, US data show that utilization rates are similar among the OPOs that mostly frequently and least frequently perform biopsies and that the observed association between a biopsy being performed and risk of nonutilization is confounded by indication since kidneys that are at an independent risk of nonuse are also more likely to be biopsied.⁹ In the United States, an increase in the recovery of kidneys from nonideal donors due to changing utilization practices and regulatory pressure on OPOs has been one driver of increasing kidney nonuse. A recent national analysis estimated that 43% of the increase in nonuse in the 2 years after the implantation of distance-based allocation was attributed to increased kidney recovery from nonideal donors.¹⁸

In a US study involving simulated organ offers to transplant physicians, offer acceptance rates for kidneys from donors with AKI were low in the absence of biopsy results but markedly increased when reassuring histology was presented.¹⁹ Similarly, a survey of hypothetical organ offers to Canadian transplant physicians showed that offer acceptance rates were not improved by not showing biopsy results when considering a marginal donor.²⁰ A UK audit similarly showed that among kidney pairs from 68 donors, utilization rates were over three-fold higher among kidneys that underwent preimplantation biopsies (61% versus 17%). The Pre-Implantation Trial of Histopathology in Renal Allografts study is a recently completed British stepped-wedge cluster randomized trial that studied whether providing centers with the ability to request preimplantation histologic assessments of kidneys from donors 60 years or older would improve the utilization of organs from these donors. This study's biopsy service used 4-mm punch biopsy sampling, rapid formalin-fixed paraffin-embedded (FFPE) processing, and remote, digital pathologist interpretation. Preprint data indicate that providing access to this service did not result in improved utilization or higher 1-year post-transplant eGFR of kidneys that were transplanted, possibly due to large intercenter variability in biopsy uptake (with one center biopsying only 1% of kidneys from eligible donors).²¹ However, when only one kidney from a pair underwent a biopsy, the biopsied kidney was significantly more likely to be used for transplant than the nonbiopsied kidney (46% versus 20%). Together, these data indicate that preimplantation biopsies might best be used to supplement clinical data primarily when clinical data are either unknown or place the kidney at high risk of nonutilization in the absence of reassuring histology.

The current practice of performing biopsies on most kidneys transplanted in the United States has several practical disadvantages. Performing biopsies in circumstances where additional histologic assessment is not needed adds cost and complexity to organ allocation. Performing and interpreting preimplantation biopsies may also increase

cold ischemia time for biopsied kidneys. An analysis of US national data demonstrated a 1-hour increase in median cold ischemia time for every 10.7% increase in the proportion of kidneys biopsied at an OPO level.¹ These indirect data may be confounded by the possibility that kidneys with undesirable characteristics are both more likely to be biopsied and also have longer allocation times due to difficulty finding an accepting center. However, although it is likely that there is some direct increase in cold ischemia time when a biopsy is performed,^{9,22} potential increases in cold ischemia time might be minimized by better coordination of the biopsy interpretation process with other clinical interventions and laboratory tests that need to be completed.

Presently, in the absence of any high-quality real-world data, best practice may be to perform preimplantation histologic assessments predominantly on kidneys that transplant centers/recipients are unwilling to use based on clinical characteristics alone, including those with limited donor clinical history, high donor serum creatinine, and/or donor history of long-standing medical comorbidities such as diabetes (Table 1). These criteria are predominantly based on expert opinion rooted in observational data with a high degree of inconsistency, indirectness, and publication bias, resulting in a quality of evidence rating of “Very Low” for all recommendations and highlighting the need for prospective data to guide preimplantation biopsy practice. Notably, a recently published pilot trial randomized deceased kidney donors who met preimplantation biopsy criteria to either immediate frozen section preimplantation biopsies or delayed permanent sections with results only available after implantation.²³ The investigators noted that trial feasibility was limited by difficulty in obtaining informed consent from waitlisted candidates, including low contact and consent rates leading to 8 hours of administrative work per consented candidate. These findings highlight the need for broad collaboration in prospective procurement biopsy studies, including consensus on the ethics of community-level consent with the option for individual candidate opt-out.

Optimizing Preimplantation Biopsy Sampling, Processing, and Interpretation

Preimplantation histopathologic assessment of deceased donor kidneys typically focuses on the degree of chronic

changes present—particularly GS, IF/TA, and arteriosclerosis and arteriolosclerosis.¹⁰ The incorporation of these elements into organ quality evaluations necessitates accurate and reproducible assessments of each histologic feature. Unlike kidney biopsies performed in other clinical settings, preimplantation biopsies are typically wedge biopsies processed as frozen section specimens and read by pathologists without specific expertise in kidney histopathology. Each of these aspects has been hypothesized to threaten preimplantation biopsy accuracy and reproducibility. A single-center US study of 606 kidneys transplanted after undergoing multiple preimplantation biopsies showed poor agreement between sequential biopsies in the assessments of GS ($\kappa=0.12$), IF/TA ($\kappa=0.12$), and arteriosclerosis ($\kappa=0.17$).²⁴ Some variability may simply reflect the focal nature of pathology, which necessitates incorporating multiple measurements of each feature and reporting of the mean, SD, and confidence intervals of the measurements.^{25–27} Multiple estimates could be rapidly obtained by digital analysis of deeper sections of the same biopsy and by pooling the results of the right and left kidneys. Furthermore, artificially low κ values stem from disagreements between degrees of chronic changes that do not have distinct clinical implications (*i.e.*, arteriosclerosis “minimal” versus “mild”).²⁸ Indeed, even among 69 transplanted kidneys that received “gold standard” per-protocol biopsies 7 and 14 days post-transplant, reproducibility of GS, IF/TA, and vascular disease was limited.²⁷

If not of sufficient depth to sample most of the cortex and deeper vessels, wedge biopsies can be biased by superficial cortical scars that result in overestimation of IF/TA. Moreover, wedge samples can yield underestimation of arteriosclerosis when taken with a pointed apex, which limits the number of arteries that can be examined. Muruve *et al.* obtained multiple sections on nine kidneys nonused due to suboptimal findings on preimplantation wedge biopsies, demonstrating that presumably superficial biopsies overestimated GS.²⁹ By contrast, a retrospective analysis of transplanted kidneys biopsied both before implantation and after reperfusion found that both wedge and needle core preimplantation biopsy results had similarly poor correlation with reperfusion GS.³⁰ The purported limitations of wedge biopsies are operator-dependent:

Table 1. Suggested deceased kidney donor criteria to prompt preimplantation histologic assessment

Criterion	Justification
Donors with elevated nadir serum creatinine (≥ 2 mg/dl) ^a Donors with a history of diabetes mellitus, poorly controlled hypertension, or hypertension with evidence of end-organ damage ^a Kidneys undergoing salvage allocation placement attempts for which transplant centers are unwilling to accept offers without histologic assessment	Use of preimplantation biopsy to “rescue” kidney that will otherwise be discarded based on clinical history and laboratory values alone
Donors with anuric AKI requiring KRT Donors with disseminated intravascular coagulation and AKI	Evaluation for infarction/coagulative necrosis suggesting low likelihood of recovery of significant kidney function
Donors with AKI with laboratory or clinical findings indicative of possible GN, vasculitis, or thrombotic microangiopathy	Identification of possible intrinsic kidney disease ^b

^aExcept in cases where the diagnosis is very recent (*e.g.*, <1 year before donation) or where a center willing to accept the organ for transplant based on other favorable clinical criteria is rapidly identified.

^bPotentially limited if relying on frozen section specimens alone.

There is no reason that wedge biopsies must be superficial or compromised by a pointed apex.²⁵ Besides needle core biopsies, skin punch biopsy technique may be an additional alternative to wedge sampling, providing higher likelihood of adequate vascular sampling and concordance with the degree of chronic changes seen on reperfusion histology in one small study³¹ and used successfully during the Pre-Implantation Trial of Histopathology in Renal Allografts trial.

Relatively few studies have compared the findings of frozen section specimens with standard FFPE specimens.^{32–34} A previous Banff Working Group study demonstrated poor interclass correlation for every aspect of frozen section specimens other than number of glomeruli, whereas FFPE specimens showed excellent or good interclass correlation for all features,³² although other studies have had contradictory findings.³³ Correlation between frozen and paraffin sections was found in the Maryland Aggregate Pathology Index study,³⁵ Parisian data,³⁶ and in Belgium.³⁷ Most other studies comparing frozen and paraffin sections have confounding factors, as that frozen sections read by nonspecialized on-call pathologists, whereas the comparison FFPE sections were assessed by specialist renal pathologists.^{38–41}

In the United States, only 49% of OPOs report that preimplantation biopsy specimens are “always” or “usually” interpreted by pathologists with kidney expertise.¹⁰ In a seminal study, Azancot *et al.* compared on-call biopsy reads for 182 extended criteria donor kidneys transplanted in Spain to subsequent rereads by renal pathologists. They found low agreement between interpretations (weighted κ 0.41) and then demonstrated that increased chronic changes as assessed by the renal pathologists—but not the on-call pathologists—was associated with inferior allograft function 1 year after transplantation.⁴² These data support routine reliance on pathologists with expertise in deceased donor kidney pathology to interpret preimplantation biopsies, potentially using telepathology services to increase availability to such expertise.^{42,43}

Evidence-Based Incorporation of Preimplantation Histology into Organ Quality Assessments

Historically, the emphasis of preimplantation biopsies was quantifying GS,⁴⁴ although this has subsequently expanded to include the routine reporting of IF/TA and vascular disease. In the United States, the Organ Procurement and Transplantation Network’s currently recommended standardized preimplantation biopsy report further includes nodular mesangial GS, cortical necrosis, and fibrin thrombi.⁴⁵ The biopsy reporting form should also have a free text area to record other sporadically encountered findings such as GN, focal segmental sclerosis, interstitial nephritis, vasculitis, and neoplasms.

A common concern regarding the use of chronic changes on preimplantation kidney biopsies to judge organ quality is that most chronic changes may simply reflect donor age, which is already accounted for as a clinical variable. Nephrosclerosis increases with age even among healthy individuals, and GFR loss with health aging seems to be attributable to nephron loss with stable single-nephron GFR.^{46–49} Furthermore, the association between

increasing age and decreasing GFR seems similar among those with and without nephrosclerosis.^{48,49} Understanding the nuance of these findings makes it clear that they do not eliminate the value of preimplantation histology. Age-related GS, *e.g.*, predominantly affects the superficial cortex, whereas pathologic GS extends into deeper areas of the cortex, suggesting that adequate sampling depth can capture clinically relevant increases in chronic changes.⁵⁰ Finally, microstructural features such as nonsclerotic glomerular tuft volume do not change with healthy aging and therefore may be incorporated in the assessment of kidney quality, perhaps with the assistance of artificial intelligence (AI).^{51,52}

Many retrospective studies have attempted to study the association between the degree of chronic changes on preimplantation kidney biopsies with post-transplant allograft longevity with mixed results. Among the largest of these reports was a US study of 4480 kidneys from extended criteria donors that underwent preimplantation biopsies during allocation.⁵³ In this study, Stewart *et al.* found an independent association between GS and allograft failure that plateaued after GS exceeded 10%. However, the latter finding was likely attributable to selection bias given a high nonutilization of kidneys with GS >10% (including 54% nonuse for GS 11%–15% and almost 86% for GS >20%). Other retrospective studies are subject to similar utilization-based selection biases, although approaches aimed at reducing selection bias corroborate the association Stewart observed.⁵⁴ These studies are additionally limited by their focus on associative modeling, while predictive modeling approaches might better elucidate whether biopsy findings add additional value to the prediction of allograft failure.

Attempts to overcome this selection bias include analyses of French and Belgian biopsy data, which are unique in that preimplantation biopsies are routinely performed, but the results are not available for organ utilization decisions. Using a derivation cohort of 1629 French allografts and a validation cohort of 1107 Belgian allografts, Reese *et al.* found no added prognostic value of preimplantation histology after accounting for donor clinical characteristics.⁵⁵ Importantly, they also demonstrated that 45% of the US kidneys for which biopsy findings were the reason cited for nonuse were able to be matched to transplanted French/Belgian kidneys, the latter of which demonstrated good post-transplant outcomes. An important caveat to these results, however, is that many of the kidneys studied have favorable clinical characteristics and likely did not represent a cohort for which the use of preimplantation biopsies may be needed to inform utilization, despite being ECD organs. While over one quarter of kidneys in both the derivation and validation cohort met ECD criteria, in the Belgian validation cohort, only 0.36% of kidneys were from donors with diabetes, mean donor age was only 48 years, and 85% of kidneys were from donors with serum creatinine <1.5 mg/dL. Correspondingly, these validation cohort kidneys had predominantly favorable histology, including 98% with IF/TA scores of 0 or 1, 98% with arteriosclerosis scores of 0 or 1, and 92% with GS $\leq$ 20%. Therefore, while this study adds strong evidence against performing biopsies on kidneys that are clearly acceptable for transplant, it is unclear whether the findings can inform

the use of preimplantation histology to guide the allocation of the subset of kidneys that will not be accepted for transplant as a strategy to “rescue” them from discard.

By contrast, Remuzzi *et al.* conducted a prospective trial in which kidneys from donors older than 60 years were allocated as single-kidney or dual-kidney transplants (or discarded) based on the degree of chronic changes on preimplantation biopsies.⁵⁶ Using this

strategy, 62 transplants using kidneys from donors in the study achieved similar outcomes to transplants using kidneys from younger donors, supporting the value of a histology-informed approach to marginal organ utilization.^{56,57} However, based on these data alone, it is unclear whether these thresholds for histology-informed utilization practices are optimized, as this study was performed when these kidneys were routinely discarded, so

Table 2. Recommendations for preimplantation biopsy sampling technique and interpretation

Recommendation 1: We recommend that preimplantation histologic assessment not be routinely performed but be reserved for deceased donor kidneys that are unlikely to be used for transplant based on donor clinical characteristics (Table 1).^{20,74} Rationale: The quality of kidneys from low-risk donors can often be confidently assessed based on clinical and laboratory parameters alone. The absence of significant chronic histologic changes on preimplantation biopsy of kidneys from clinically higher-risk donors can “rescue” deceased donor kidneys that will otherwise not be accepted for transplant Quality of supporting evidence: Very low Data need: There is a need for randomized trials to assess the effect of preimplantation biopsy on utilization practices among kidneys at the highest risk for discard Recommendation 2: We suggest that attention be paid to sample adequacy while performing a preimplantation biopsy, rather than insistence on a specific biopsy technique. Wedge biopsies should be 1.0 cm wide, 0.5 cm in thickness, and 0.5 cm in depth, with straightened edges and a rounded base to minimize overrepresentation of superficial cortex.²⁵ Needle biopsies should have a minimum of 25 glomeruli,⁷⁵ which can be attained by taking two 16-gauge cores from the cortex. Punch biopsies should measure 0.4 cm in diameter and 0.8 cm in depth and bisected with the two inner surfaces embedded to cut to increase sampling²¹ Rationale: There is no evidence to suggest superiority of any tissue sampling method if sample adequacy is achieved Quality of supporting evidence: Very low Data need: Head-to-head trial comparing the association of preimplantation histology obtained through each sampling method with post-transplant outcomes Recommendation 3: We do not recommend any specific preparation and staining techniques for preimplantation kidney biopsies Rationale: No prospective studies have compared frozen section specimens with rapidly processed FFPE specimens. H&E is the commonest stain used in clinical practice; interpretation is confounded by freezing artifact. It is plausible that incorporation of PAS and trichrome staining protocols for frozen sections or using rapid FFPE sections would improve the assessment of chronic changes and other key findings Quality of supporting evidence: Very low Data need: Comparison of association of preimplantation histology processed by frozen sections and rapid FFPE, with and without additional stains, with post-transplant outcomes, including an assessment of cost and potential increase in cold ischemia Recommendation 4: We suggest that preimplantation biopsies should be interpreted by pathologists with dedicated training/expertise in deceased donor kidney pathology Rationale: Biopsy reads from renal pathologists show stronger associations between biopsy findings and post-transplant kidney allograft outcomes^{42,43} Quality of supporting evidence: Very low Data need: None Recommendation 5: We recommend that incorporation of preimplantation biopsy results in overall assessments of organ quality account for donor characteristics including age and comorbidities, kidney function, hypertension, diabetes, infectious risks, and ApoL1 status, if known. Strict histologic cutoffs to inform utilization (e.g., GS <20%) should be avoided Rationale: Chronic changes increase with age and comorbidities, so consideration of biopsy findings should avoid “double counting” donor history and the presence of age-appropriate chronic changes. No histologic algorithm has shown to be sufficiently accurate in predicting allograft outcomes. Paired kidney studies have demonstrated that transplanted contralateral mates to kidneys that were nonused due to biopsy findings often have good allograft longevity Quality of supporting evidence: Very low Data need: Test and validation cohorts enriched for moderate-to-severe lesions should be studied by predictive modeling to develop updated pretransplant estimates of the risk of allograft failure. These models should integrate quantitatively assessed continuous lesion scores with attached confidence intervals, clinical data, perfusion pump parameters, urine or tissue biomarkers, emerging radiologic studies (e.g., MRI), and recipient factors. Currently used decision thresholds, such as those in the Remuzzi system, have not been optimized and should be reset based on such predictive modeling Recommendation 6: We recommend incorporation of whole slide imaging into the workflow for assessing preimplantation biopsies Rationale: Digital pathology could allow access to remote nephropathologists with a high degree of expertise, as well as rapid access to second opinions during allocation. Continued improvement in digital algorithms will likely soon enable tissue morphometry and deep learning techniques to facilitate automated segmentation and identification of stain-independent pixel-level imaging features that correlate with organ quality Quality of supporting evidence: Very low Data need: Although segmentation of normal and sclerotic glomeruli is now quite reliable, there is still need for substantial improvement in digital quantitation of IF and TA. Arteries can now be accurately recognized as objects, but training datasets that adequately represent the spectrum of donor arterial and arteriolar pathology have not yet been assembled and the ability to interpret/exclude tangential sections needs to be developed
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FFPE, formalin-fixed paraffin-embedded; GS, glomerulosclerosis; H&E, hematoxylin and eosin; IF, interstitial fibrosis; MRI, magnetic resonance imaging; PAS, periodic acid-Schiff; TA, tubular atrophy.

low “safe” thresholds were used. In 2012, it was identified that a Remuzzi score (sum of GS, TA, IF, and vascular score) of 4 had similar graft survival in single transplants compared with ≤ 3 ,⁵⁸ with some centers changing to a modified cutoff of 4 between single and dual transplants,⁵⁹ confirming these findings. An Austrian study subsequently found that a Remuzzi score ≤ 6 was suitable for single kidneys.⁶⁰ Kidneys transplanted without the use of preimplantation biopsies and found to have Karpinski scores (equivalent to Remuzzi scores) of ≥ 6 had a 5-year death-censored graft survival $>80\%$,⁶¹ although numbers in this category were relatively small. This UK-based study also found that had preimplantation biopsies been used for kidney utilization based on the modified Remuzzi cutoffs of 0–4 single, 5–6 double, and ≥ 7 discard, 29% fewer patients would have received transplants and 33 of the

125 (26.4%) kidneys transplanted and functioned well would have been inappropriately wasted.⁶¹ Together, these data argue that the Remuzzi cutoffs remain too low and cannot be interpreted as strict thresholds to guide allocation decisions.

Conclusions and Future Directions

Ultimately, the limited availability of high-quality, prospective studies of preimplantation biopsies restricts the development of evidence-based consensus on best practices for their performance and interpretation, although recommended best practices based on available data are presented in Table 2. It is unclear whether obtaining preimplantation biopsies has a net negative effect on kidney utilization, but it seems likely that favorable findings—

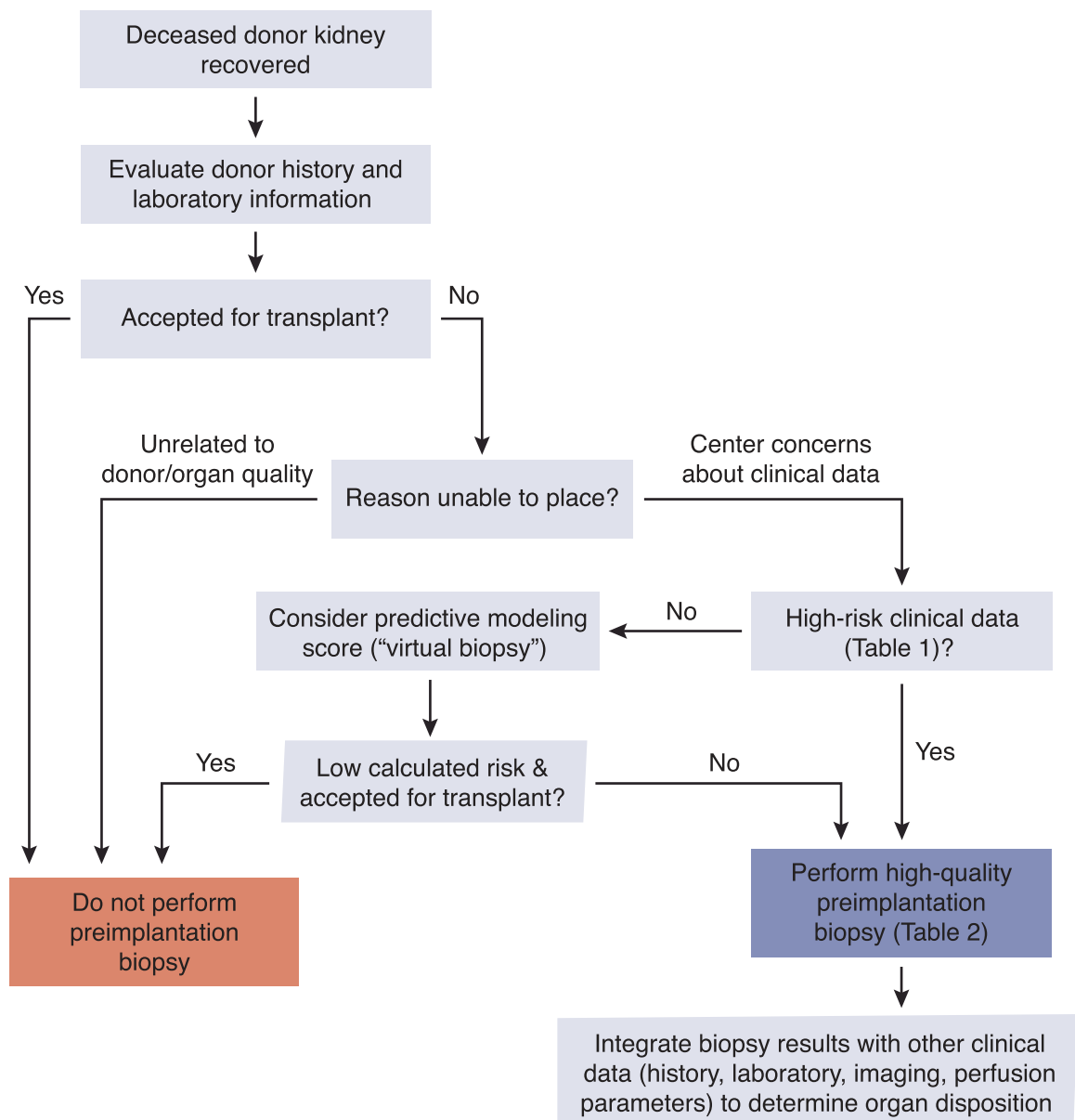


Figure 1. Proposed algorithm for incorporating preimplantation biopsies into the evaluation of deceased donor kidneys during allocation.

such as mild chronic changes—can reassure clinicians who are otherwise hesitant to use a kidney from a marginal donor. While there is low-quality evidence that preimplantation biopsy findings are poorly reproducible, these data come from retrospective cohorts that are enriched for a lack of reproducibility by selection bias and predominantly include grade 0 and 1 histologic lesions of limited significance. Moreover, these studies cannot inform us regarding the reproducibility of findings when interpreted by experienced renal pathologists. Finally, concerns about the inability of preimplantation biopsies to provide independent prognostic information also have limited support based primarily on retrospective studies that do not focus on predictive modeling. Based on currently available data, an approach to integrating preimplantation biopsies into the evaluation of deceased donor kidneys may focus on kidneys at risk of nonuse without histologic assessment (Figure 1).

“Virtual biopsies” (prediction models of underlying histology based on clinical factors) may also help integrate clinical findings when assessing organ quality,⁶² with ongoing refinement using AI to identify low-risk cases whereby a preimplantation biopsy might be omitted.⁶³ Future studies should determine the additive value of generating the virtual scores as opposed to proceeding with the transplant entirely on the low-risk nature of the clinical variables⁶⁴. In a dataset that did not include nonutilized organs, the false-positive rates for moderate/severe pathology lesions were 18.6% for IF/TA, 21.6% for arteriosclerosis, and 26.8% for arteriolar hyalinosis, while the sensitivity for detecting moderate/severe lesions was moderate.

Emerging literature on the ability of AI to augment pathologists’ interpretation of kidney biopsy samples suggests that such technology could be used to improve biopsy speed and reliability, including the use of automated segmentation technology and automatically generated preliminary reads.⁶⁵ AI may also allow the identification of novel aspects of biopsies to be considered, as well as allow more granular interpretation such as the assessment of IF as a continuous variable, estimation of TA based on quantifiable measurements of tubular basement membrane thickening and wrinkling, and vascular segmentation with corrections for tangential sectioning.^{66–70} However, digital algorithms to quantify interstitial and vascular pathology are still in need of substantial improvement, and preanalytic, interplatform, interscale, and interalgorithm variability also remain limiting.^{70–73}

Further research is also needed to determine how best to incorporate biopsy results into the overall prediction of post-transplant allograft function—particularly since the reliability and prognostic value of a biopsy may differ based on how it was performed and interpreted. In addition, emerging evidence has shown potential benefit from using additional noninvasive measures of organ quality, such as urinary/perfusate concentrations of kidney injury, fibrosis biomarkers, and novel imaging techniques. Proposals to develop an “enhanced KDPI” that integrates donor clinical information alongside other parameters such as biopsy results, perfusion pump parameters, biomarkers, and recipient information warrant further study as a means of facilitating the synthesis of a large volume of donor/organ data, particularly in circumstances when

these are conflicting. A historical reliance on explanatory models may also be replaced with a predictive modeling framework, where allograft failure risk estimates (such as the kidney donor risk index) are replaced with models that integrate all donor and organ information—all of which interact with each other to predict allograft outcomes. This approach would improve the clinical value of preimplantation biopsies and also allow the study of whether biopsy results improve the predictive value of models derived from other available information, either among all kidneys or among a subset of kidneys where donor history is limited or conflicting.⁶⁵ Such an approach will also require the use of large, heterogeneous datasets to develop and validate accurate classifiers that can be presented during organ offers to aid organ offer decisions.⁶⁵

Ultimately, transplant outcomes are inherently uncertain, and even evidence-based incorporation of histology in deceased donor kidney assessment will not enable perfect prediction of post-transplant allograft function. Nevertheless, a commitment by funding agencies to supporting pragmatic, cluster-randomized trials may allow an emergence from the reliance on low-quality retrospective data to guide optimization of preimplantation biopsy practices (Table 2). Such trials may include comparing frozen section specimens with rapid FFPE specimens; the use of additional stains; comparing standard on-call biopsy reads with those by experienced experts through the use of high-quality telepathology network; and incorporating AI techniques to determine the effect on organ utilization and association with post-transplant outcomes. The optimization of biopsy technique and interpretation using head-to-head trials would also advance our understanding of how best to integrate preimplantation biopsy results with other clinical data. Importantly, consideration should be given to conducting these studies with cohorts enriched for moderate-to-severe grade lesions obtained from multiple centers. This would hopefully provide sufficient data to justify raising the current chronicity threshold scores for organ acceptability. The accumulation of such evidence must be paired with better education of transplant professionals on the need to abandon using traditional utilization criteria and instead replace these binary “Go/No go” biopsy thresholds with incorporation of histologic findings into holistic assessments of overall organ quality.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/JSN/F327>.

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