

**OPTN Kidney Transplantation Committee
Biopsy Best Practices Workgroup
Meeting Summary
September 14, 2021
Conference Call**

Andrew Weiss, MD, Chair

Introduction

The Biopsy Best Practices Workgroup (the Workgroup) met via teleconference on 09/14/2021 to discuss the following agenda items:

1. Review Project Timeline
2. Literature Review

The following is a summary of the Workgroup's discussions.

1. Review Project Timeline

The Workgroup reviewed the project scope, goals, and timeline leading up to public comment.

Summary of discussion:

The Workgroup had no questions or comments.

2. Literature Review

The Workgroup discussed their review of the literature surround procurement kidney biopsies and the guided questions provided.

Data Summary:

Discussion questions – Minimum Donor Criteria Appropriate for Biopsy

- Do you think requiring procurement biopsies would alter the kidney discard rate, increase or decrease?
 - How can biopsies be utilized to lower the discard rate? To promote “ruling in” as opposed to “ruling out”?
 - What are the characteristics of kidneys that would benefit from the additional information provided by procurement biopsies?
- What kinds of kidneys are more likely to be biopsied, and which kinds are more likely to be discarded? What kinds of kidneys should be biopsied?
 - Can biopsies provide reliable critical information about increased risk of graft failure that could prevent negative recipient outcomes?
 - Vice versa, can biopsies provide reliable, critical information about potentially reduced risk of graft failure that could prevent unnecessary organ discard?

Discussion questions – Standardized Pathology Report

- Which biopsy parameters are most helpful to organ evaluation? Which are most predictive of graft outcomes?

- How does biopsy information provide additional insight to clinical evaluation? Does it help better inform donor-recipient matching or post-transplant recipient care?
- What information is critical to understanding the quality of a biopsy?
- Why are some biopsy parameters more “reproducible” than others? How can this be adjusted for, particularly in reporting, to improve reproducibility and reliability amongst biopsy information utilized to evaluate deceased donor kidneys?
 - Given how much weight is put on glomerular sclerosis, should certain thresholds be set (such as less than 15 glomeruli) to denote certain biopsies or samples as less reliable?
 - Beyond a standardized set of histological characteristics, how could biopsies and biopsy reporting be standardized to maximize usefulness and efficiency?

Summary of discussion:

The Chair described the *Can Behavioral Research Improve Decision Making*¹ study, noting specifically that acute kidney injury (AKI) type kidneys saw nearly a four-fold increase in offer acceptance with a good biopsy compared to no biopsy. High kidney-donor profile index (KDPI) and low creatinine type kidneys, there was little difference in offer acceptance between no biopsy and a “good” biopsy, but a large drop in offer acceptance for “poor” biopsy results. The Chair added that these kinds of kidneys often performed well as grafts, and remarked that in instances where a kidney has relatively good kidney function, a biopsy could be resulting in increased discards instead of acceptances. Another member pointed out that Stewart et al.² also finds significant variation in offer acceptance within the same programs, between clinicians. Members of the same program or team may have different philosophical drivers for acceptance. The Chair agreed there was considerable subjectivity in the acceptance, and suggested that acute renal failure and AKI kidneys would be a good area to focus on in terms of standardizing biopsy performance, since the rate of turn down significantly decreases with a reassuring biopsy. The other member agreed.

One member remarked that the Stewart et al.³ study pointed out that biopsies tend to be used to rule out rather than rule in, at least for the non-AKI kidneys. Another member shared that Lentine et al. (2019)⁴ looked at organ procurement organization (OPO) practices with biopsy and discard rates, and found that low KDPI kidneys (less than 20 percent) that were biopsied had a significantly higher discard rate than those that were not biopsied. The member continued that this likely pointed to AKI, since it would be rare to biopsy such a low KDPI kidney in a non-AKI setting. The member suggested that this confounding by indication in suggesting that performing biopsies on low KDPI kidneys lead to increased discard. The member noted that Lentine et al.⁵ did not discuss the biopsy findings that could have led to discard, as the study was a large-sample data analysis.

The Chair remarked that Stewart et al.⁶ found a higher rate of discard associate with high glomerular sclerosis in the low creatinine, high KDPI kidney scenario. The Chair noted that, considering the findings of the Lentine et al.⁷ study, it could be detrimental to biopsy younger donors with AKI. However, the

¹ Darren Stewart et al., *Can Behavioral Research Improve Transplant Decision-Making? A Mock Offer Study on the Role of Kidney Procurement Biopsies* (Kidney 360, American Society of Nephrology, 2020)

² Ibid

³ Ibid

⁴ Krista Lentine et al., *Variation in Use of Procurement Biopsies and its Implications for Discard of Deceased Donor Kidneys Recovered for Transplantation* (American Journal of Transplantation, American Society of Transplantation, 2019)

⁵ Ibid

⁶ Stewart et al., *Can Behavioral Research Improve Transplant Decision-Making? A Mock Offer Study*, 2020

⁷ Lentine et al., *Variation in Use of Procurement Biopsies*, 2019

Chair inferred that there could be benefit to performing biopsy for slightly older donors with AKI, since centers would likely turn them down without reassuring biopsy information.

Staff asked the Workgroup what characteristics AKI kidneys and donors with AKI would have that would indicate a biopsy could be necessary or helpful to placement. One member shared that lack of a normal creatinine in younger donors is indicative. The member gave an example: a young donor with an initial creatinine of 2 or 2.5 milligrams per deciliters (mg/dL) that increases to 8.0 mg/dL, and then goes on dialysis are particularly concerning. Similarly, a donor with an initial creatinine of 3.0 and a terminal creatinine of 5.0 should be biopsied over a donor with an initial creatinine of 0.7 and a terminal creatinine of 5.0. The latter donor's recorded normal range creatinine value is reassuring, and a biopsy may not be necessary. The Chair agreed, noting that for donors who never have a normal range creatinine, it is difficult to differentiate between AKI or chronic kidney disease (CKD) causing high creatinine values. The Chair added that the initial creatinine sometimes could be more important than the age of the donor, and gave an example. A 30-year old donor with a history of intravenous drug use who had an initial creatinine of 2.0 and a terminal creatinine of 3.5 would warrant a biopsy, particularly because there are risk factors. The Chair continued that it is difficult to know whether the donor arrived at the hospital with acute renal failure or just general had a higher baseline creatinine of 2.0.

One member shared that, based on her review of the literature, it seems that biopsies generally lead to rule out, and that biopsy information would be more likely to tip the scale to decline than to accept. Another member shared that he'd read the same, particularly in Reese et al.'s article⁸, which provides an international comparison of biopsy practices between US and European kidneys. The member expressed a concern with the methods presented in that article, pointing out that matching along histologic findings wasn't sufficient matching, and the match US kidneys tended to have much higher rates of diabetes and hypertension.⁹ The member continued, remarking that it was likely that biopsy information was used in conjunction with other clinical parameters, and that biopsy findings themselves were not solely used to discard in all cases. The study positioned the information to imply the US discarded a thousand useable kidneys, but didn't appropriately regard the other factors centers may have considered in declining. The member added that this Workgroup has discussed these projects in terms of utilizing biopsy information to best match kidneys to potential recipients. For kidneys from donors with a history of hypertension and diabetes and a normal biopsy, it may not be the best organ for the recipient at the top of the match run, but it could get appropriately matched to another potential recipient further down the match. The Chair remarked that Stewart et al.¹⁰ concluded that biopsy could predispose to turn downs in some scenarios, but that biopsies could increase rate of acceptance for AKI kidneys.

Staff asked the Workgroup what kinds of kidneys are more likely to be biopsied, which are more likely to be discarded, and what characteristics are common between those two. One member shared that it is easy to come up with hard rules for older donors and DCDs, but AKI kidneys with age and circumstances are more difficult. The Chair remarked that the minimum criteria currently in development by the Workgroup have focused on characteristics of kidneys that would be more predisposed to discard without a biopsy. The Chair continued that the next step to that would be using the biopsy results then to focus on how to allocate as opposed to discarding, such as setting kidneys up to be allocated first as dual rather than single. Another member agreed, noting that allocation would be quicker down a dual

⁸ Peter Reese et al., *Assessment of the Utility of Kidney Histology as a Basis for Discarding Organs in the United States: A Comparison of International Transplant Practices and Outcomes* (Journal of the American Society of Nephrology, 2021)

⁹ Ibid

¹⁰ Stewart et al., *Can Behavioral Research Improve Transplant Decision-Making? A Mock Offer Study*, 2020

kidney list, particularly with more information. The member compared such kidneys to those that perform poorly on the pump – it can be tricky to decide whether or not to transplant it with certain patients. The member asked, if the biopsy doesn't correlate with original clinical findings, are people more or less likely to use it? The member continued, suggesting that biopsy information is really more confirmatory and is additional, helpful information. The criteria developed by the Workgroup focused on biopsy for kidneys for which more information is useful.

One member remarked that practically, requiring biopsy could cause delays that contribute to cold time accumulation, which can also result in increased chance of discard. Another member agreed, recommending that biopsies could be required only if requested, so that OPOs don't need to biopsy if procuring or accepting teams don't feel a biopsy is necessary. The member added that this still could be challenging, particularly in broader allocation. The Chair explained that requiring biopsies would make it difficult for OPOs to default to not performing biopsies. A member responded that many OPOs are happy to perform biopsies, and noted that it would be difficult to refuse a biopsy if it's been requested by a center interested in accepting the organ, as it can increase the likelihood of placement. Requiring biopsy when an accepting center doesn't want a biopsy performed, similarly to pumping, could negatively impact acceptance. One member referenced the Lentine et al. study, which found that biopsy rates across OPOs ranged from 22.8 percent to 77.5 percent, a huge variation in practices.¹¹ Another member commented their experience has been that some OPOs refuse to biopsy some kidneys, even if a center requests it. The Chair commented that this variation in OPO practice is one reason uniform donor criteria appropriate to initiate biopsy would be helpful in standardizing biopsy practice.

The Chair agreed that the literature provides evidence to steer away from performing biopsies on certain kidneys, particularly those with good kidney function, but remarked that those kinds of kidneys are not included in the criteria developed by the Workgroup so far. Most donors with less than 1.5 mg/dl creatinine don't necessarily need a biopsy, particularly those with a KDPI less than 85 percent and that don't qualify as an expanded criteria donor (ECD). The Chair continued that in many ways, this literature provides support for the criteria the Workgroup has previously discussed. The Chair suggested that if more AKI kidneys were biopsied, fewer would be declined, which could potentially impact discard rates.

One member shared that, as OPOs become more aggressive in their approach to procuring organs and working with donors, the non-transplant rate may not necessarily decrease. The best donors are easily identified, and it's the more challenging donors that present an opportunity for growth for OPOs. The member continued that it is often implied that the discard rate represents well-functioning, good kidneys, which is not the case. The member pointed out that many of these kidneys are not in great shape, adding that discard can be appropriate in some cases.

The Chair described the article *Procurement Biopsies in the Evaluation of Deceased Donor Kidneys* by Carpenter et al., highlighting the finding that correlations between frozen wedge procurement biopsies and formalin-fixed paraffin-embedded (FFPE) reperfusion biopsies were poor.¹² The biopsies were scored, separating kidneys into "optimal" and "suboptimal" categories based on degree of inflammation, sclerosis, interstitial fibrosis, tubular atrophy, and vascular disease. The Chair shared that agreement between procurement and reperfusion biopsies was poor, even between suboptimal and

¹¹ Lentine et al., *Variation in Use of Procurement Biopsies*, 2019

¹² Dustin Carpenter et al., *Procurement Biopsies in the Evaluation of Deceased Donor Kidneys* (Journal of the American Society of Nephrology, 2018)

optimal categorization.¹³ The Chair shared that the study also found no correlation between procurement biopsies and graft outcomes, but correlation between core needle FFPE biopsies read by renal pathologists and graft outcomes.¹⁴ The latter biopsy readings are not necessarily available at the time of offer decision making. Another member referenced Azancot et al.'s article from 2013, which found no association between readings performed by on-call pathologists and graft outcomes, but did find association between readings performed by renal pathologists and graft outcomes.¹⁵ The member suggested that the lack of association with graft outcomes of procurement biopsies could be related to the training of the pathologists performing the reading.

The Chair referenced Carpenter et al.'s findings from 2018, noting that there was the largest discrepancy in agreement for degree of glomerulosclerosis, the biopsy parameter that is considered most in organ offer evaluation.¹⁶ The Chair pointed out a need for centralized reading that would allow OPOs and transplant centers to easily access pathologists with renal-specific training. The Chair explained that the current approach of having on-call pathologists perform procurement biopsy readings is producing information that may not be accurate. The Chair added that the information needs to be reproducible. One member cited the Liapis et al.'s *Banff Histopathological Consensus Criteria for Preimplantation Kidney Biopsies*¹⁷, commenting even renal pathology experts could not always necessarily agree. The member continued that organ offer decisions could be based on incomplete or unreliable information, and adding that the US transplant system likely already performs too many biopsies, though it would be difficult to stop performing biopsies overall.

The Chair noted that having centralized, system access to renal pathologists for procurement biopsy readings would likely be a sticking point in the community feedback. The Chair suggested including this as an addendum to the project recommendations.

Staff commented that, previously, the Workgroup had made specific design choices to allow both renal and non-renal pathologists to appropriately and accurately categorize and report the degree of specific parameters. Staff asked how reproducibility and variation in readings could be addressed in other ways. The Chair agreed that the current design of the standardized pathology report is a good start, adding that the data collection aspect itself will also be helpful.

A HRSA representative recommended that Workgroup members share the drafted standardized pathology report with their on-call and transplant pathologist colleagues, to get their feedback. The Chair agreed that this would be a good suggestion, and noted that the Workgroup utilized the renal pathologist's subject matter expertise to guide discussion and decision-making, particularly in determining what kinds of information general pathologists can reasonably and accurately provide.

Upcoming Meeting

September 27, 2021 – Teleconference

¹³ Ibid

¹⁴ Ibid

¹⁵ M. Antonieta Azancot et al., *The Reproducibility and Predictive Value on Outcome of Renal Biopsies from Expanded Criteria Donors* (Kidney International, 2013)

¹⁶ Carpenter et al., *Procurement Biopsies in the Evaluation of Deceased Donor Kidneys*, 2018

¹⁷ H. Liapis et al., *Banff Histopathological Consensus Criteria for Preimplantation Kidney Biopsies* (American Journal of Transplantation, 2017)

Attendance

- **Committee Members**
 - Andrew Weiss
 - Catherine Kling
 - Jim Kim
 - Julie Kemink
 - Meg Rogers
- **HRSA Representatives**
 - Jim Bowman
 - Marilyn Levi
- **SRTR Staff**
 - Bryn Thompson
 - Jonathan Miller
 - Raelene Skerda
- **UNOS Staff**
 - Lindsay Larkin
 - Amanda Robinson
 - Kayla Temple
 - Leah Slife
 - Nicole Benjamin
 - Ross Walton