OPTN Kidney Committee
Biopsy Best Practices Workgroup
Meeting Summary
June 28, 2021
Conference Call

Andrew Weiss, MD, Chair

Introduction

The Biopsy Best Practices Workgroup (the Workgroup) met via teleconference on 06/28/2021 to discuss the following agenda items:

1. Welcome and Updates
2. Review Project Timeline
3. Standardized Biopsy Report Review
4. Data Standards Checklist: Standardized Biopsy Report

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

1. Welcome and Updates

The Workgroup was informed of OPTN Executive and Policy Oversight Committees' approval of both Workgroup projects.

Summary of Discussion:

The Workgroup had no questions or comments.

2. 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.

3. Standardized Biopsy Report Review

The Workgroup reviewed the draft Standardized Biopsy Report, discussing feedback provided by a renal pathology subject matter expert and adjusting for clarity and consistency.

Summary of discussion:

One member recommended altering the Percent Glomerulosclerosis parameter's response option from categories of percentages to a free-text number field, since the Number of Glomeruli and Number of Sclerosed Glomeruli parameters were already present on the form. The Workgroup Chair agreed, adding that this particular element was critical to evaluation as well. Another member agreed. Staff asked the Workgroup to consider how precisely the percent glomerulosclerosis can be measured, and a workgroup member clarified that pathologists use exact counts of sclerosed and non-sclerosed glomeruli to calculate the percentage of glomerulosclerosis.

A member suggested aligning the order of "Present" and "Absent" response options for clarity and consistency. The Workgroup agreed.

One member recommended removing the "focal and diffuse" definitions from beneath the Cortical Necrosis and Fibrin Thrombi parameters, particularly since these binary definitions provide less useful and granular information than the pathologist provides with a percentage estimate. This is particular true as 40 percent and 10 percent Cortical Necrosis are very different indicators, but are technically characteristically focal. The Workgroup agreed.

One member asked the Workgroup about continuing to leave interstitial inflammation out of the standardized report. The parameter could be semi-quantitative in response options, but is difficult to consistently estimate on frozen sections. The member continued that an estimated interstitial inflammation from a frozen section will likely generally be the same as the estimate for fibrosis. The Chair agreed, adding that interstitial inflammation is not particularly critical as a parameter. The Chair continued, recommending the addition of a free-text response "Other Comments" box to allow a pathologist to provide additional information in necessary cases. Another member agreed, remarking that interstitial inflammation could introduce significant noise for pathologists trying to distinguish inflammation and scarred areas. For particularly striking findings not communicated in other sections of the report, the pathologist could utilize the "other comments" section. Other members agreed with this recommendation.

4. Data Standards Checklist

The Workgroup applied the OPTN Data Advisory Committee's data standards checklist to the standardized biopsy report, assessing the report and the proposed elements for relevancy, purpose, and reliability.

Data Summary:

Data Standards Questions:

- What is the intent or purpose of collecting this specific data element?
- Does the data element measure what it intends to measure?

Summary of discussion – Relevancy and Purpose Questions:

Staff utilized the biopsy type and tissue preparation technique parameters to provide an example response to the relevancy and purpose questions. These elements are intended to inform on the sample type and preparation, and provide necessary information on external factors influencing histological examination.

The Chair remarked on the rarity of formalin-fixed paraffin-embedded (FFPE) biopsy samples read and reported on in real time post-procurement. Another member agreed, adding that it was also rare for transplant programs to have staff available to prepare FFPE samples on a routine basis. One member pointed out that organ procurement organizations (OPOs) and transplant programs sometimes get FFPE sample readings 24 to 48 hours post-procurement, and that information should be reported and shared. The Chair suggested keeping the tissue preparation technique element for documentation within the standardized biopsy report, particularly to allow for appropriate differentiation between frozen and FFPE samples.

The Workgroup achieved consensus that the biopsy type and tissue preparation technique elements are intended to indicate sample type and preparation, and are appropriate measures for these parameters.

The Workgroup Chair pointed to the literature on procurement kidney biopsy's lack of reproducibility, difficulty in determining parameters most critical to long term graft outcomes, and use in offer evaluation, and noted that percent glomerulosclerosis consistently shows correlation with long term graft outcome. The Chair continued that the number of glomeruli, number of sclerosed glomeruli, and

percent glomerulosclerosis are data elements critical to kidney offer evaluation. The number of glomeruli in particular also indicates the quality of the biopsy and potentially its reproducibility. A member agreed, and pointed out that these elements are some of the more objective and measurable parameters.

Staff asked the Workgroup what the percent glomerulosclerosis parameter measures, and what the intent of collecting this on a biopsy report would be. A member explained that many diseases impacting kidney function, such as hypertension and diabetes, can lead to sclerosis of the glomeruli, leading to poor glomerular filtering and thus reduced kidney function. The Chair added that glomerulosclerosis, interstitial fibrosis, and tubular atrophy are often final common pathways of chronicity, and that these parameters are measured to gauge how well the kidney graft will function and how long it may survive. The Chair also noted that any number of disease processes can filter down into glomerulosclerosis. Another member agreed. One member added that the number of glomeruli, the number sclerosed, and percent glomerulosclerosis essentially help project the number of functioning nephrons the kidney may have, which can determine, along with the size of the recipient, the estimated creatinine six months or a year post-transplant if the graft survives.

One member asked the workgroup how well a kidney would function in a recipient if kidney function is normal in the donor and there is 20 or 30 percent glomerulosclerosis found on the biopsy. A member responded that a 70 year old donor with lean muscle and normal creatinine may still present with significant sclerosis – indicating that this kidney may not function well in a 40 year old muscular male recipient. The Chair added that a donor's serum creatinine may overestimate kidney function, particularly if the daily solute load or creatinine generation is not high. The Chair continued that a slender 70 year old donor may not produce much creatinine to filter through, and the deceptively low serum creatinine may overestimate kidney function as a graft.

The Workgroup achieved consensus that the number of glomeruli, number of sclerosed glomeruli, and percent glomerulosclerosis are intended to indicate the degree of chronic damage to the kidney, which will impact its function as a graft. The number of glomeruli are also intended to indicate the general quality and reproducibility of the biopsy sample. The Workgroup agreed that these data elements are good measures of this chronic damage, and communicate what they are intended to communicate.

A member remarked that Interstitial Fibrosis and Tubular Atrophy (IFTA) and Vascular Disease are terminal pathways of chronic damage to the kidney, given that all compartments of a kidney are interconnected. IFTA indicates the degree of wear and tear of chronicity on the kidney, and the vascular damage (or vascular sclerosis) can provide a sense of the risk of further scarring, as narrower vessels will have more difficulty perfusing the kidney with the lumen narrowed by chronic changes. Another member agreed.

The Workgroup Chair pointed out that few transplant centers have cut offs for these elements, but that the IFTA and vascular damage parameters are important to the larger picture of the graft itself. A member agreed, adding that the granularity in the lower end of the response categories is critical to detecting differences, and will be helpful to have on hand going forward.

The Workgroup Chair asked the Workgroup about the reproducibility of the IFTA and vascular disease parameters on a frozen section sample, and pointed out that it would still likely be fairly obvious to a pathologist if a kidney presented with less than 5 percent IFTA or 10 percent, or even greater than 50 percent. A member agreed, adding that none of these are perfect measures, particularly on a frozen section. The member continued that though these measures of chronic organ damage seem redundant, these slightly different measures are critical together to produce a holistic picture of kidney function. The Workgroup Chair agreed.

The Workgroup achieved consensus that the Interstitial Fibrosis and Tubular Atrophy (IFTA) and Vascular Disease elements measure chronic damage to a kidney, particularly chronic wear and tear and risk of future scarring in chronically narrowed vessels. These elements are appropriate measures for these parameters.

One member remarked that Nodular Glomerulosclerosis is another pattern of chronic injury to the kidney, typically due to long standing hyperglycemia. More specifically, these are leaky glomeruli that can become problematic once filtering in the recipient. The Workgroup Chair added that this parameter is helpful particularly for patients who have long histories of diabetes without diagnosis or management. The Chair continued that this is an important indicator of chronicity and potentially the amount of time the disease process has been ongoing.

The Workgroup agreed that Nodular Glomerulosclerosis is a measure of chronic damage to the kidney that can indicate reduced kidney graft function, and that this is an appropriate measure of this parameter.

The Workgroup Chair explained that the cortex is a functional part of the kidney where the glomeruli are, and noted that necrotic material there can indicate acute damage with no expectation of recovery. The Chair continued that the degree of Cortical Necrosis is critical to kidney evaluation, and can indicate the kind of damage sustained by the kidney through the death and procurement process. One member agreed, adding that cortical necrosis is an acute finding often indicative of non-viability of the organ, due to the irreversibility of the damage. Another member noted that Cortical Necrosis and Fibrin Thrombi both indicate acute damage, and can signal potential evolutionary damage upon reperfusion that the kidneys may get worse. The Chair commented that the cortical necrosis and fibrin thrombi are the "tip of the iceberg" as far as acute damage.

The Workgroup achieved consensus that Cortical Necrosis and Fibrin Thrombi are appropriate measure acute and irreversible damage to the kidney, and can also indicate potential worsening of kidney function upon reperfusion.

<u>Data summary:</u>

Reliability Questions:

- Is the source of information objective and reliable?
- Is the element designed to consistently reproduce the same results?
    - Are there objective measures that could be considered rather than having a user calculate or interpret information prior to reporting?
    - If calculation cannot be avoided, are there different methods or calculations used to obtain this data element? If so, is it clear which method/calculation should be used?
- Is the data element definition sufficiently clear and precise to enable consistent entry?

<u>Summary of discussion:</u>

Staff utilized the biopsy type and tissue preparation technique parameters to provide an example response to the reliability questions. The Chair remarked that reliability can be difficult to gauge with biopsies given extensive literature questioning the general reproducibility and reliability of the procurement biopsies themselves. Staff clarified that these questions are simpler to address element by element – explaining that an objective and reliable source is one from which the same, correct answer will consistently be given. One member noted that, for biopsy type and tissue preparation technique, the source of information is reliable, the elements are designed to consistently reproduce the same results, and the definitions are sufficiently clear to enable consistent entry. The member continued that in particular, it will be clear between wedge or core and frozen or FFPE samples. The Chair agreed.

The Workgroup achieved consensus that the biopsy type and tissue preparation technique data elements have an objective and reliable source, are consistently designed to reproduce the same results, and are sufficiently clear and precise to enable consistent entry.

One member remarked that while the pathology literature will provide the most insight regarding reliability of counting sclerosed and non-sclerosed glomeruli, these particular elements are relatively reliable and objective. Another member added that these elements have the least interobserver variability according to the literature.

A member asked how reliability would be impacted if it were a pathologist with less renal experience performing the reading. Another member responded that most pathologists are at least used to reading kidney specimens, for tumor or otherwise, and are comfortable differentiating between open and sclerotic glomeruli. The member continued that some of the other parameters are much more open to operator-dependent variables, such as whether a pathologist has nephron training.

Staff clarified that some aspects of the reliability questions deal not just with reproducibility, but also the general source itself. Staff provided an example, noting doctor reading an echocardiogram is generally more reliable than a family member uncertain of a donor's medical history.

The Chair asked the Workgroup whether percent glomerulosclerosis should be categorized, including considerations about research assessment and continuous data points. One member remarked that researchers can always categorize and group absolute percentages. Staff added that the percentage would need to be calculated ahead of categorization anyway. The Chair noted that the calculated percent glomerulosclerosis is important to evaluation. Another member added that the percentage calculation is the only way to find this number, and that the calculation is simple enough to reasonably include.

The Workgroup achieved consensus that the number of glomeruli, number of sclerosed glomeruli, and percent glomerulosclerosis elements have an objective and reliable source, are consistently designed to reproduce the same results, and are sufficiently clear and precise to enable consistent entry. The Workgroup achieved consensus that the calculation required for the percent glomerulosclerosis data element cannot be avoided, but that it is clear and simple which calculation should be required.

The Chair remarked that IFTA and vascular damage elements are more influenced by the pathologist reading it, and added that it would be difficult to regulate the training of the pathologist performing the reading. One member responded that most decision making occurs at the extreme ends for vascular damage and IFTA, and that these elements are more reproducible as a result of that. The member continued that the categorization of responses for these elements made them more reproducible and reliable as well. The Chair agreed, noting that these categories seem appropriate for attaining and maintaining improved reliability and reproducibility.

The Workgroup achieved consensus that the interstitial fibrosis and tubular atrophy and vascular damage elements have an objective and reliable source, are consistently designed to reproduce the same results, and are sufficiently clear and precise to enable consistent entry.

The Chair noted that the cortical necrosis, fibrin thrombi, and nodular glomerulosclerosis elements were set up well. Another member agreed, noting that indication of these elements at all can be generally troubling.

Staff asked the workgroup to consider the open text percentage field in regards to reliability and reproducibility. One member responded that cortical necrosis is often a glaring finding, and so estimation will be easier and more reproducible. The member continued that fibrin thrombi can be counted, and so the percentage calculation should be reliable, objective, and reproducible.

The Workgroup achieved consensus that the cortical necrosis, fibrin thrombi, and nodular glomerulosclerosis elements have an objective and reliable source, are consistently designed to reproduce the same results, and are sufficiently clear and precise to enable consistent entry.

A member asked whether the discussions regarding the data standards checklist are annotated and submitted by the Workgroup, and staff clarified that they will maintain notes and documentation of group discussions and conclusions developed in working through the checklist. Staff also clarified that these discussions will be captured in the written proposal and board briefing documents.

One member asked about the Banff renal biopsy criteria, and how that applies to this workgroup's discussions. Another member explained that while the Banff criteria encompasses some of these chronic findings, they were established to standardize assessment for rejection, rather than baseline graft characteristics. The Workgroup concluded th variables are not necessarily applicable to this work, as the Workgroup is not focused on rejection assessment. The Workgroup Chair added that literature involving the Banff criteria is included in the initial set of literature reviewed and discussed by the Workgroup.

Upcoming Meeting

August 3, 2021 – Teleconference

Attendance

- **Committee Members**
  - Andrew Weiss
  - Catherine Kling
  - Colleen O'Donnell Flores
  - Dominick Santoriello
  - Jim Kim
  - Mark Orloff
  - Meg Rogers
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
- **SRTR Staff**
  - Bryn Thompson
  - Jon Miller
  - Nick Salkowski
- **UNOS Staff**
  - Lindsay Larkin
  - Amanda Robinson
  - Ross Walton
  - Ben Wolford
  - Kayla Temple
  - Lauren Motley
  - Leah Slife
  - Savannah Holmes
  - Nicole Benjamin