

Briefing Paper

Guidance for Transplant Program Participation in the Transplantation of non-A1/non-A1B (A2/A2B) Donor Kidneys into Blood Group B Candidates

OPTN/UNOS Minority Affairs Committee

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Guidance for Transplant Program Participation in the Transplantation of non-A₁/non-A₁B (A₂/A₂B) Donor Kidneys into Blood Group B Candidates

<i>Affected Policies:</i>	<i>N/A</i>
<i>Sponsoring Committee:</i>	<i>Minority Affairs</i>
<i>Public Comment Period:</i>	<i>July 31, 2017 – October 2, 2017</i>
<i>Board of Director's Date:</i>	<i>December 4-5, 2017</i>

Executive Summary

Blood type B candidates, a blood group more common in underrepresented minorities, have longer kidney waiting times. In December 2014, the new Kidney Allocation System (KAS) became effective, including *Policy 8.5.D: Allocation of Kidneys by Blood Type*, which allows for blood types A, non-A₁ and AB, non-A₁B kidneys to be transplanted to blood type B recipients who meet certain criteria.¹ Allocation of deceased donor kidneys from blood group A, non-A₁ and AB, non-A₁B to blood group B kidney recipients has improved transplant rates among disadvantaged blood group B patients with equivalent long-term graft outcomes compared to blood type compatible transplants.^{2, 3} However, the 18 month KAS post-implementation data analysis revealed that, despite these comparable outcomes, an overwhelming majority of transplant programs (82 percent) do not perform any non-A₁/non-A₁B (A₂/A₂B) transplants and that overall transplant programs have not taken advantage of this policy change.⁴ Further, a 2016 OPTN/UNOS Minority Affairs Committee (MAC) survey to all active U.S. kidney transplant programs revealed that many programs cited difficulty in establishing a protocol for patient enrollment as the major barrier to performing these transplants. Specifically, the transplant programs identified the following obstacles when developing the required protocols to participate in non-A₁ transplants:

- Difficulty establishing titer thresholds (32 percent)
- Difficulty developing an informed consent policy (21 percent)
- Difficulty determining patient eligibility (18 percent)

OPTN/UNOS policy allows each transplant program to develop and implement protocols for determining candidate eligibility, but many established programs follow similar practices for protocol.

Based on the survey findings, these best practices are offered in a guidance document as an effort to increase the number of kidney transplant programs that perform non-A₁/non-A₁B (A₂/A₂B) transplants. An increase in the number of programs using this provision can increase equity in access to transplants for disadvantaged blood group B candidates, due to a greater number of potential donor matches.

What problem will this resource address?

Blood group B candidates typically experience longer waiting times than blood groups AB and A, with the majority of waitlisted blood group B candidates classified as minority. Based on OPTN data as of June 9, 2017, blood type B candidates ever on the kidney waiting list in 2016 were composed of 72.7% minority

¹ OPTN Policies, Section 8.5D: Allocations of Kidney by Blood Type

² Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. *Clin Transplant* 2016; 30:589-597

³ Williams WW, Cherikh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. *AJT* 2015; 15:3134-3142.

⁴ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

candidates, defined as Black, Asian, Hispanic, American Indian/Alaska Native, Native Hawaiian/other Pacific Island, and multiracial candidates. Based on these statistics, there is a strong potential to reduce waiting time and increase the number of transplants for blood group B candidates, if transplant programs take advantage of the policy permitting blood types A, non-A₁ and AB, non-A₁B kidneys to be transplanted to eligible blood type B recipients.

The policy permits these type of transplants under the following conditions:

Kidneys may be transplanted into candidates with blood type B who meet all of the following criteria:

- 1. The transplant program obtains written informed consent from each blood type B candidate regarding their willingness to accept a blood type A, non-A₁ or blood type AB, non-A₁B blood type kidney.*
- 2. The transplant program establishes a written policy regarding its program's titer threshold for transplanting blood type A, non-A₁ and blood type AB, non-A₁B kidneys into candidates with blood type B. The transplant program must confirm the candidate's eligibility every 90 days (+/- 20 days).⁵*

Despite this policy, the vast majority of blood type B candidates have not been indicated in UNetsm as willing to accept a subtype-compatible kidney, and the majority of transplant programs do not perform these type of transplants.⁶ There has been a very small increase in transplants for this population since the implementation of the KAS in 2015, despite much larger potential.

A 2016 survey, conducted by the MAC workgroup, indicates that non-participant programs request protocol and testing guidance to implement the provision. The Committee's intent is to suggest protocol guidance to increase the number of programs participating in the voluntary provision to allow non-A₁/non-A₁B (A₂/A₂B) donors to match with blood group B candidates.

Why should you support this resource?

Non-A₁/non-A₁B (A₂/A₂B) to B blood group B kidney transplantation has improved transplant rates among disadvantaged blood group B patients with equivalent long-term graft outcomes.^{7,8} OPTN data collected 6 months post-KAS indicated very few (447 of 11,182, or 4.0%) active blood type B registrations were listed as eligible and willing to accept a subtype non-A₁/non-A₁B (A₂/A₂B) kidney. Far more have been reported as ineligible (16.4%), while the majority still have unknown status (79.2%).⁹

OPTN data collected 18 months post-KAS indicates a majority of transplant centers (82%) do not perform non-A₁/non-A₁B (A₂/A₂B) to blood type B transplants.¹⁰

Before a transplant center may perform non-A₁/non-A₁B (A₂/A₂B) to blood type B transplants, it must develop a protocol for these transplants. In July 2016, the Committee conducted a survey to learn about transplant programs' barriers for registering their blood type B candidates as eligible to receive offers from non-A₁/non-A₁B (A₂/A₂B) donors. (Figure 1)

⁵ OPTN Policies, Section 8.5D: Allocations of Kidney by Blood Type

⁶ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

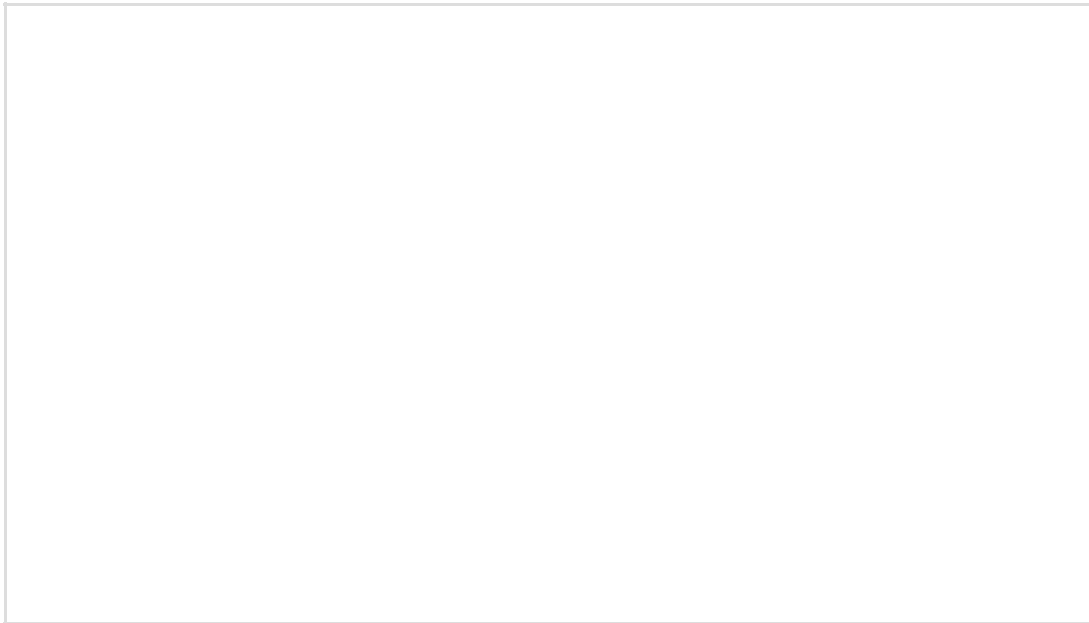
⁷ Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. Clin Transplant 2016; 30:589-597

⁸ Williams WW, Cherikh WS, Young CJ et al.

⁹ OPTN/UNOS Report: Kidney Allocation System (KAS). "Out-of-the-Gate" Monitoring Report, 6/5/2015.

¹⁰ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

Figure 1: Which of the following could help you establish an A2/A2B into B blood type protocol at your center?



Non-participant center respondents cited difficulty in developing protocols, including development of titer thresholds and an informed consent policy. A majority of non-participant center respondents stated that guidance for best practices would be helpful in non-A₁/non-A₁B (A₂/A₂B) to blood type B participation. Based on these results, the Committee developed this guidance.

How was this resource developed?

A June 2015 progress review of the Kidney Allocation System (KAS) demonstrated that few transplant programs were registering their blood type B candidates as eligible for non-A₁/non-A₁B (A₂/A₂B) offers, despite the new provision in KAS permitting such transplants.

UNOS staff indicated that the lack of available lab facilities in certain regions and the additional cost of titer tests to match a greater number of donors to potential recipients may be impediments to program participation. Feedback from fall 2015 regional meetings suggested that the OPTN should encourage more programs to participate in the non-A₁/non-A₁B (A₂/A₂B) to blood group B candidate provision.

After reviewing this evidence, the MAC discussed sponsoring a project to provide guidance or education to programs wishing to obtain greater access for blood group B candidates. The MAC formed a workgroup in October 2015 to begin gathering information on why transplant programs do not participate in the provision. The workgroup included members of Minority Affairs, Kidney, and Transplant Administrators (TAC) Committees. The Histocompatibility Committee declined to participate, but offered to review any work outcome.

The workgroup reviewed OPTN data and research literature indicating various reasons to explain why centers were not participating in the provision, and eventually decided to deploy a survey to kidney transplant program administrators. Over the next several months, staff and the workgroup developed approximately ten survey questions to gather data on the number of programs participating, and to understand why eligible programs are not participating and what would encourage them to become participants.

The electronic survey was sent to all kidney program administrators in July 2016. The response rate was 22 percent. Results indicated a desire to create a guidance document (see Figure 1 above) to advise centers on implementation of the provision. The workgroup agreed and also supported an effort to create an educational resource to complement guidance.

While the workgroup drafted recommended protocols in the winter and spring of 2017, the workgroup's survey results were presented during an oral session at the Transplant Management Forum (April 2017) and as a poster presentation at the American Transplant Congress (May 2017).¹¹

Workgroup meetings centered on discussion of the protocol development, including titer testing, candidate informed consent, and confirmation of candidate eligibility to receive organ offers. The workgroup felt that more specific expertise was required to draft the titer threshold considerations and the titer variability guidance, so input from a blood bank administrator, followed by review from the Histocompatibility Committee leadership was requested. The workgroup accepted the draft titer protocol offered.

Kidney Committee leadership reviewed the draft guidance and suggested some additional citations to data evidence, while one Kidney Committee member questioned adding any titer level recommendations at all. The MAC feels that providing titer limits is integral to providing guidance to implement the provision. Histocompatibility leadership added language to this section to reassure the institutions that OPTN/UNOS policy allows each transplant program to develop and implement its own approach for ascertaining the appropriate method and threshold.

The MAC voted to distribute the guidance for public comment on June 8, 2017 (Yes - 10, No - 0, Abstain - 0).

How well does this resource address the problem statement?

The Committee believes this guidance document will increase the number of programs performing non-A₁/non-A₁B (A₂/A₂B) to blood group B transplants, therefore increasing the number of transplants for this disadvantaged group.¹² If the transplant rate for blood group B candidates is increased, their wait time should be reduced, providing greater equity in access for these candidates.¹³

Average Wait Time by Blood Type

Candidate Blood Type	Average Waiting Time (in years)
AB	2
A	3
O	5
B	6

As of the 6-month post-KAS implementation report, 47 non-A₁/non-A₁B (A₂/A₂B) to blood group B transplants had occurred during the six months after KAS implementation compared to just six over the six months prior to KAS.¹⁴ This guidance suggests protocols for titer testing, consent development, and routine update of candidate eligibility can increase the rate of transplants among candidates. The suggestions are based on survey results and the practices of established programs, but may not be ideal for all circumstances or cases. Expenses to establish and maintain the provision may vary among programs.

Was this proposal changed in response to public comment?

Public comment was sought on this guidance document from July 31, 2017 to October 2, 2017. This proposal was widely supported in public comment, including all regional meetings and presentations to

¹¹ Transplant Management Forum 2017. [Link to conference agenda.](#)

¹² Williams WW, Cherkh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. *AJT* 2015; 15:3134-3142.

¹³ Hart A, Smith JM, Skeans MA, et al. *Kidney*. *AJT* 2016; 16, s2: 11-46.

¹⁴ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

three OPTN committees. Professional groups and individuals also submitted supportive comments, some with suggested enhancements, on the proposal. Respondents agreed that the guidance responds to the major obstacles identified by transplant programs as barriers to implementing a non-A₁/non-A₁B to B protocol, and that implementation of the guidance can have significant potential beneficial effects, creating more potential matches for the blood type B disadvantaged populations. Additional themes identified in public comment included:

1. Requests for education for transplant program staff and patients about how to manage any potential complications from transplanting non-A₁/non-A₁B (A₂/A₂B) kidneys to blood type B candidates
2. Frustration with the requirement to acquire additional patient informed consent to match blood type B to non-A₁/non-A₁B (A₂/A₂B) donors, even though the match is considered compatible
3. Requests for separate detailed protocol guidance for currently waitlisted candidates and new candidates for the match

The Committee discussions surrounding these themes are detailed below.

1. Education on Increased Risk

The MAC workgroup members and staff found no literature during proposal development providing evidence of increased risk associated with transplanting non-A₁/non-A₁B (A₂/A₂B) kidneys to blood type B candidates.

2. Informed Consent and Increased Complication Risk

Informed consent is currently required per current policy and therefore it is included in the guidance document. The Committee agrees that it may be advantageous to eliminate the need for additional informed consent, which may inadvertently cause patients and transplant programs to be concerned that these types of transplants are at increased complication risk. The MAC and UNOS staff reviewed the published literature and found no evidence of increased risk for blood type B candidates to receive non-A₁/non-A₁B (A₂/A₂B) kidneys. While changes to the policy are out of scope for this proposal, the MAC will collaborate with the Histocompatibility or Kidney Committees to attempt to change this requirement, should one of those Committees decide to pursue it. As stated above, the MAC also determined that education about complications would not be added at this time, since no literature about increased complications was found.

3. Protocol Guidance

The MAC intends to provide encouragement and suggested guidance for centers to develop protocol that works best, without the perception of creating policy. With this intention, the MAC did not add protocol information for outside labs performing titer testing monitoring antibodies post-transplant, as suggested by the Kidney Committee. The Committee also encourages centers to develop more detailed guidance to distinguish testing protocol for waitlisted and new candidates.

The MAC made a few non-substantive changes for style, clarity, and consistency, as well as several additional supporting references and some grammatical changes. The Guidance remains consistent in content with the version distributed for public comment.

The MAC approved this guidance and recommended consideration by the OPTN/UNOS Board of Directors during an October 2017 meeting by a teleconference vote (Yes - 11, No - 0, Abstain - 0).

Which populations are impacted by this resource?

Based on OPTN data as of June 9, 2017, blood type B candidates ever on the kidney waiting list in 2016 were composed of 72.7% minority candidates, defined as Black, Asian, Hispanic, American Indian/Alaska Native, Native Hawaiian/other Pacific Island, and multiracial candidates. There is a strong potential to reduce waiting time and increase transplants for this population by matching the more common non-A₁/non-A₁B (A₂/A₂B) to blood group B candidates, based on these statistics.

How does this resource impact the OPTN Strategic Plan?

1. *Increase the number of transplants:* There is no evidence that implementation of the guidance will increase the number of transplants overall, but if more programs participate in this KAS provision, a greater number of non-A₁/non-A₁B (A₂/A₂B) to blood group B transplants may result.
2. *Improve equity in access to transplants:* The primary intent of this guidance is to increase equity in access to transplants for the disadvantaged blood group B recipients, with a high percentage of minorities, experiencing longer wait times.
3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* Wait time for the less common blood group B candidates, experiencing longer wait times, may decrease if a greater number of donor matches exist.
4. *Promote living donor and transplant recipient safety:* There is no impact to this goal.
5. *Promote the efficient management of the OPTN:* There is no impact to this goal.

How will the OPTN implement this resource?

Due to community interest in this topic, an instructional program, spotlighting established programs matching non-A₁/non-A₁B (A₂/A₂B) to blood group B candidates, will be developed if the guidance is approved by the Board. The OPTN will communicate this new information through TransplantPro and the OPTN website, linking the information to related guidance, as well. The instructional program would be housed on UNOS Connect and promoted through all available and appropriate channels.

How will members implement this resource?

Transplant Hospitals

If programs choose to develop protocols consistent with this guidance, they must work closely with labs to implement the provision and to establish titer levels for candidate eligibility. Additional staff effort includes a greater amount of time per candidate to provide education on protocol and to periodically reconfirm candidate eligibility. New costs will exist for additional tests to match candidates with donors and to reconfirm candidate eligibility while wait-listed.

Histocompatibility Laboratories

Labs must work closely with their respective renal transplant program(s) to establish a policy that indicates the appropriate titer levels for determining candidate eligibility and defines the frequency of titer testing. New costs will exist for the additional testing, while total cost will depend on the recommended frequency of testing for a given candidate. Additional staff time may be needed to pull samples to send to a local blood bank for testing.

There is no impact on OPO members.

Will this resource require members to submit additional data?

No additional data submission will be required at this time.

How will members be evaluated for compliance with this resource?

Guidance from the OPTN does not carry the weight of policies or bylaws. Therefore, members will not be evaluated for compliance with this document.

How will the sponsoring Committee evaluate whether this resource was successful post implementation?

It is not possible to establish a causal relationship between a change in the number of programs participating in the non-A₁/non-A₁B (A₂/A₂B) to blood group B provision and the release of this guidance document and corresponding education/outreach. In order to assess if the guidance and related education/outreach has positively impacted disadvantaged blood group B candidates, the Committee will monitor the number of programs participating in this provision and the median waitlist time for blood type B candidates. This data is currently compiled as part of the monitoring plan for the KAS and reported every six months. UNOS staff will report this information to the Committee at six-month intervals following consideration by the Board. This guidance will be updated as needed based on review by experts in the field.

Guidance Document

Guidance for Transplant Program Participation in the Transplantation of Non-A₁/Non-A₁B (A₂/A₂B) Donor Kidneys into Blood Group B Candidates

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Summary and Goals

Blood type B candidates, a blood group more common in underrepresented minorities, have longer kidney waiting times. In December 2014, the new Kidney Allocation System (KAS) went into effect, including *Policy 8.5.D: Allocation of Kidneys by Blood Type*, which allows for blood types A, non-A₁ and AB, non-A₁B kidneys to be transplanted to blood type B recipients who meet certain criteria.¹ Allocation of deceased donor kidneys from blood group A, non-A₁ and AB, non-A₁B to blood group B kidney recipients has improved transplant rates among disadvantaged blood group B patients with equivalent long-term graft outcomes compared to blood type compatible transplants.^{2 3} However, the 18 month KAS post-implementation data analysis revealed that an overwhelming majority of transplant programs (82 percent) do not perform any non-A₁/non-A₁B (A₂/A₂B) transplants and that overall transplant programs have not taken advantage of this policy change, which provides greater access to deceased donor kidneys for disadvantaged blood group B candidates.⁴ Further, a 2016 OPTN/UNOS Minority Affairs Committee (MAC) survey to all active U.S. kidney transplant programs revealed that many programs cited a difficulty in establishing a protocol for patient enrollment as the major barrier to performing these transplants. Specifically, the transplant programs identified the following obstacles when developing the required protocols to participate in non-A₁ transplants:

- Difficulty establishing titer thresholds (32 percent)
- Difficulty developing an informed consent policy (21 percent)
- Difficulty determining patient eligibility (18 percent)

Based on these survey findings, these best practice guidelines are offered in an effort to increase the number of kidney transplant programs that perform non-A₁/non-A₁B (A₂/A₂B) transplants.

¹ OPTN Policies, Section 8.5D: Allocations of Kidney by Blood Type

² Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. *Clin Transplant* 2016; 30:589-597

³ Williams WW, Cherikh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. *AJT* 2015; 15:3134-3142.

⁴ Aeder, Mark. The New Kidney Allocation System (KAS): The First 18 Months. Prepared for OPTN Minority Affairs In-Person Meeting, September 20, 2016.

33 Background

34 One of the factors impacting access to transplantation is candidate blood type, and it has been well-
35 established that blood group O and B candidates have longer waiting times as shown in the table below.⁵

Candidate Blood Type	Average Waiting Time (in years)
AB	2
A	3
O	5
B	6

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37 Blood group B candidates comprise 16 percent of candidates listed on the kidney transplant waiting list
38 per OPTN data as of November 14, 2016, but received only 13 percent of the total kidney transplants
39 between January 1, 2015 and September 30 2016. Furthermore, because blood group B candidates on
40 the kidney waiting list in 2016 were composed of 72.7 percent minority candidates, defined as Black,
41 Asian, Hispanic, American Indian/Alaska Native, Native Hawaiian/other Pacific Island, and multiracial
42 candidates, this disparity affects minority populations most of all.

43 Multiple studies have demonstrated the safe and effective transplantation of blood group B kidney
44 transplant recipients with kidneys from donors having the less immunogenic, non-A₁ subtype. Equivalent
45 long-term graft outcomes have been demonstrated after the transplantation of non-A₁/non-A₁B (A₂/A₂B)
46 donor kidneys into blood group B recipients as compared to blood type compatible transplantation^{6,7,8,9,10}.
47 As such, the new kidney allocation system (KAS) included the provision to allow non-A₁ transplants to
48 blood group B recipients to provide better equity among candidate blood types, which likely includes
49 minority groups disadvantaged on the transplant waiting list. According to an 18-month KAS post-
50 implementation analysis, there has been an increase in non-A₁/non-A₁B (A₂/A₂B) deceased donor kidney
51 transplants, but still many candidates who could benefit from these transplants are not registered for
52 these organs.¹¹ Compared to the 19 (0.2 percent) non-A₁/non-A₁B (A₂/A₂B) transplants performed 1-year
53 pre-KAS, there were 179 (1.0 percent) performed in the 18-months post-KAS, a 5-fold increase. Despite
54 these gains, OPTN data available on April 30, 2017, shows that only 7.8 percent of active blood group B
55 candidates on the kidney waiting list were registered as eligible for these transplants.

56 Recommendations for Protocol Development

57 Participant transplant programs must develop a program-specific written protocol in order to receive offers
58 of non-A₁ deceased donor kidneys for their blood group B candidates. This written protocol must include:

- 59 **1. The maximum titer levels for candidate eligibility**
- 60 **2. The process for obtaining informed written consent from each blood group B candidate for**
61 **acceptance of a non-A₁ kidney**
- 62 **3. Confirmation of each candidate's eligibility every 90 days in UNetsm**

63 The guidelines below for developing each of these protocol requirements are based on MAC survey
64 results, literature reviews, sample policy, and informed consent forms provided by several transplant
65 programs that are already performing these transplants.

⁵ Hart A, Smith JM, Skeans MA, et al. *Kidney*. AJT 2016; 16, s2: 11-46.

⁶ Forbes RC, Feurer ID, Shaffer D.

⁷ Bryan CF, Cherikh WS, and Sesok-Pizzini DA. A2/A2B to B renal transplantation: past, present, and future directions. *AJT* 2016; 16: 11-20.

⁸ Bryan CF, Winklhofer FT, Murillo D, Ross G, et al. Improving access to kidney transplantation without decreasing graft survival: long-term outcomes of blood group A2/A2B deceased donor kidneys in B recipients. *Transplantation* Jul 2005 15;80(1):75-80.

⁹ Bryan CF, Shield CF, Nelson PW, et al. Transplantation rate of the blood group B waiting list is increased by using A2 and A2B kidneys. *Transplantation* 1998; 66: 1714-1717.

¹⁰ Williams WW, Cherikh WS, Young CJ et al.

¹¹ Aeder, Mark.

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1) Titer Testing of the Blood Group B Candidate

OPTN/UNOS policy allows each transplant program to develop and implement its own approach for ascertaining the appropriate method and threshold for anti-A titers used in determining candidate eligibility. The information below is summarized from published literature and is provided for informational use only.

Most programs perform anti-A₁ titer typing through their local hospital blood bank and use different methods for titer detection. The majority of respondent transplant programs participating in the survey use an anti-A titer cutoff of 1:8 as acceptable for candidate eligibility, but it is up to an individual program to determine titer thresholds. Some programs are more comfortable using a more stringent cutoff of 1:4 to determine candidate eligibility, and it is worth noting that the original outcomes data used this more stringent titer threshold. To confirm eligibility, the survey showed that most programs require two consecutive titer results.

Specific Considerations for Labs Performing Titer Testing:

The identification of red blood cell antibodies as IgM or IgG provides useful information. DTT (dithiothreitol) has been used in blood banking for decades to distinguish one type of antibody from the other since DTT can inactivate IgM in the patient's serum; however, it does not interfere with IgG. Therefore, since IgM is the predominant Ig subclass of anti-A produced by blood group B individuals, the use of DTT in the patient's serum sample and in controls is necessary to distinguish between the two types of antibodies. The use of serial dilutions with and without DTT on patient serum and controls such as anti-P1 antisera, high IgG control, and IgM control are necessary to prove that the titer of anti-A determined is indeed an IgM. Note that early studies demonstrating the success of non-A₁ kidneys into B recipients used predominantly IgG titers.

Specific Considerations for Titer Testing:

- High control IgG: is an IgG antibody that should result in a titer >8 before DTT treatment and not be reduced after DTT treatment, maintaining a titer >8.
- High titer IgM antibody control is an IgM antibody that should result in a titer of >8 without DTT treatment and be reduced by DTT treatment to a titer <8.
- Anti-P1 antisera is a low level IgM antibody that should have a positive result undiluted and be reduced by DTT treatment to a negative result.

The use of AHG (anti-human globulin) is not necessary to determine IgM titers; however, some programs might be concerned with low titer anti-A₁ IgG that the B recipient might produce. AHG simply increases the sensitivity or detection of low titer IgG antibodies only. This is called the indirect antiglobulin or Coombs Test.

Titer Variability:

Antibody titer reproducibility intra and inter laboratory is still a major concern. The lack of reagent standardization and the multiple methods in use contribute to titer variability among labs. In an effort to control such variability, Thorpe et al reported on an international collaborative study using a World Health Organization (WHO) reference reagent to try to standardize hemagglutinin testing for anti-A and anti-B titers in serum and plasma.¹² In this study where 300 samples were tested among 24 laboratories in different countries, they reported an 8 to 64 fold variation in titers per preparation and methods across laboratories. However, the intra-laboratory variability was generally good with over 90 percent of replicate titers within a 2 fold range.

The problem with such a wide variability among laboratories is multi-factorial. There is no standardized procedure; there are multiple methods (gel vs. tube), diluent, incubation times, cutoff reading and testing cell among others. The College of American Pathologists (CAP) proficiency

¹²Thorpe SJ, Fox B, Sharp G, White J, Milkins C. A WHO reference reagent to standardize haemagglutination testing for anti-A and anti-B in serum and plasma: international collaborative study to evaluate a candidate preparation. Vox Sang.2016 Aug; 111(2):161-70

111 testing titer surveys from 2014-2016 indicate that the gel method produces a closer range in variation
112 when compared to the tube method.¹³ The gel method has shown to be more consistent and more
113 sensitive and less subjective than the tube method, according to the American Association of Blood
114 Banks (AABB). However, the gel tube method for A subgroup typing of samples is not yet approved
115 by the FDA. Laboratories that want to use this method for A subgroup typing must validate the
116 protocol for its use.

117 **2) Obtaining Candidate Informed Consent for Acceptance of Non-** 118 **A₁/non-A₁B (A₂/A₂B) Type Kidneys**

119 The following items should be included in the protocol for obtaining candidate informed consent:

- 120 • Create a general statement about why it is advantageous to receive offers of non-A₁/non-A₁B
121 (A₂/A₂B) deceased donor kidneys, emphasizing that blood group B candidates have historically
122 the lowest rate of transplant. In addition, a statement regarding the similarity between transplant
123 outcomes with non-A₁/non-A₁B (A₂/A₂B) donation to B blood group recipients should be included.
- 124 • Include both the risks and benefits. Benefits could include more organ offers, with the possibility
125 of an earlier transplant. Risks should include that participants are always at risk for rejection but
126 there is no current evidence that the risk for rejection is higher in blood group B recipients with
127 low anti-A IgG titer who have received non-A₁/non-A₁B (A₂/A₂B) kidneys in comparison to blood
128 group B matched kidneys.¹⁴
- 129 • Include a statement on how often you will require the recipient to come in for a blood draw to
130 obtain anti-A titers.
- 131 • Include a statement that the program has explained the nature, risks, and benefits to accepting
132 non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys and has answered all of the candidate's
133 questions.

134 The candidate, as well as the program representative obtaining consent, must sign the form. It is also
135 recommended that candidates be informed of additional program-specific care requirements that may
136 come along with acceptance of a non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys (for example,
137 additional blood draws, biopsies).

138 **3) Confirming Eligibility to Receive non-A₁/non-A₁B (A₂/A₂B)** 139 **Deceased Donor Organ Offers**

140 Programs must confirm non-A₁/non-A₁B (A₂/A₂B) eligible candidates every 90 days in UNet. A
141 transplant program has discretion for how frequently titers are re-checked. Some programs require
142 confirmatory titer testing every 90 days for eligibility, while other programs perform testing less
143 frequently, in addition to UNet confirmation every 90 days.

¹³2014-2016 Proficiency Testing Surveys, College of American Pathologists. www.cap.org. Web. September 2017.

¹⁴Bryan C.F., Cherikh W.S., Sesok-Pizzini D.A. A2/A2B to B Renal Transplantation: Past, Present, and Future Directions. American Journal of Transplantation. 2015 Nov 10

Summary Chart: Non-A₁/non-A₁B (A₂/A₂B) Protocol Development Recommendations

Protocol Requirements	Key Components	Examples of Program Variability
Maximum Titer Levels	<ol style="list-style-type: none"> 1. Titer testing methodology (see “Specific Considerations for Labs”) 2. Establish titer cutoff (discretion of transplant program) 3. Confirm eligibility 	<p>≤ 1:4 (more stringent) 1:8 (most common) ≥ 1:16 (less stringent)</p> <p>Two consecutive titer levels</p>
Consent Development	<ol style="list-style-type: none"> 1. Develop statement about why it’s advantageous to receive offers of A₁/non-A₁B (A₂/A₂B) deceased donor kidneys 2. Develop statement of risks/benefits 3. Develop statement on specified requirements for maintaining eligibility 4. Create statement of acknowledgement by both patient and physician 	<p>Frequency of lab draw</p>
Routine Update of Candidate Eligibility (UNet)	<p>Confirmation of eligibility every 90 days</p>	<p>Either of the following:</p> <ul style="list-style-type: none"> • Repeat titer testing every 90 days • Less frequent titer testing (semiannual, annual), but with UNet confirmation every 90 days

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Possible Financial Implications and Other Concerns

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In order to begin transplantation of non-A₁/non-A₁B (A₂/A₂B) deceased donor kidneys into blood group B candidates, there is a modest financial investment at start-up followed by ongoing expense for each candidate. The following table describes the approximate resources that are needed to prepare your program for implementation. Expenses will vary from program to program and are intended as a framework for beginning analysis within your own program. You could adopt best practices from other programs, which could markedly reduce the initial investment.

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All pre-transplant efforts should be considered for reimbursement under the Medicare cost report and included in your institution’s standard acquisition charge for kidney transplants. The remainder of the services should be reimbursed through third party payers as customary and contracted by your institution.

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157 **Resource Summary:**

Potential One-Time Implementation Staff Effort:	Potential Recurring Per Patient Effort:
<ul style="list-style-type: none"> ✓ Review of draft protocols ✓ Protocol development ✓ Development of informed consent document ✓ Coordination with blood bank to educate and clarify blood use and typing ✓ Coordination with histocompatibility laboratory to establish order set, non-A₁ titer process and associated EMR (Electronic Medical Record) changes as needed ✓ Training development ✓ Staff training 	<ul style="list-style-type: none"> ✓ Description ✓ Education of patient ✓ Consent of patient ✓ Pre-authorization for non-A₁/non-A₁B titer test (IgG titration) ✓ Standing order placement for quarterly non-A₁/non-A₁B titers (IgG titration) ✓ Review and UNetsm reporting of non-A₁/non-A₁B titers at evaluation and confirmation every 90 days ✓ Non-A₁/non-A₁B titer testing for both evaluation and maintenance

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159 **Conclusion**

160 One of the primary goals of the KAS is to broaden patient access for historically disadvantaged kidney
 161 transplant candidates, which includes blood group B candidates, who have experienced greater waiting
 162 times compared to other blood groups. Available data support that access to non-A₁/non-A₁B (A₂/A₂B)
 163 donor kidneys has improved transplant rates for blood group B candidates and has effectively shortened
 164 wait times for this population.^{15 16} Use of the non-A₁/non-A₁B (A₂/A₂B) provision for blood group B
 165 candidates is not automatic and requires transplant program protocol development and maintenance. The
 166 guidelines provided in this document will aid transplant programs interested in protocol development.

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¹⁵Forbes RC, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. Clin Transplant 2016; 30:589-597

¹⁶Williams WW, Cherikh WS, Young CJ et al. First report on the OPTN national variance: Allocation of A2/A2B deceased donor kidneys to blood group B increases minority transplantation. AJT 2015; 15:3134-3142.