CareDx Perspective on
Questions for CAC on the use of Molecular Diagnostic Testing to identify acute rejection with AlloMap in Kidney Transplant recipients

1. Is there sufficient evidence to identify the patient population where molecular diagnostic test should be used? Based on the evidence, the appropriate patient population includes

Yes. AlloMap Kidney has been developed and validated as an indicator of immune status in two large prospective multi-center studies (DART, OKRA) that cover a representative sampling of the population as well as added single-center studies. The studies included all adult kidney transplants (including re-transplants) except multi-organ recipients, pregnant patients and patients <7 days post transplant. (Akalin 2021, Cheung 2022). The two multi-center studies were designed to enroll patients at centers across the country with widely differing demographics. In the Akalin 2021 validation there were 32% non-white, 63% male, and a median age of about 54. In Cheung 2022 there were 49.6% non-white, 61.7% male, and median age at enrollment of 54.

2. Is there sufficient evidence on the clinical context (i.e. for-cause vs surveillance) in which the molecular diagnostic test should be used

Evidence clearly indicates both for-cause and surveillance use. In the clinical validation study AlloMap differentiated between rejection and quiescence and rejection was shown to be different from all three definitions of quiescence, non-rejection surveillance biopsy, non-rejection for-cause biopsy, and healthy stable recipients without a biopsy (Akalin 2021).

3. In the existing evidence, what is the level of confidence (or certainty) regarding test performance data reported without any confidence intervals

There is high confidence in the ability of AlloMap Kidney to perform as published. The Cheung 2022 publication includes an extensive analytical validation that demonstrates the technical precision of the test in addition to the precision of replicate samples. Total variability was reported as lower than 5% CV. Additionally, the two publications (Akalin 2021 and Cheung 2022) both demonstrated strong differentiation between rejection and quiescence.

4. Is there sufficient evidence to support the utility of surveillance (i.e. not for-cause) testing in kidney transplant recipients

Yes. Both publications demonstrate that biopsy-proven rejection can be differentiated from quiescence, whether defined by biopsy (surveillance or for-cause) or stable healthy recipients.

4b) If yes, what is the appropriate testing schedule based on the published evidence

DART samples were generated with a schedule comprising monthly from months 1-4, then month 6 and quarterly thereafter. OKRA samples were generated on a similar schedule, although there was variance as centers were contributing to observational validation of AlloMap Kidney alongside their chosen patient testing for AlloSure.

5. Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to discriminate acute T-cell mediated rejection from quiescence

Yes. The data from both Akalin 2021 and Cheung 2022 show significant ability to differentiate all rejection from quiescence. In Akalin 2021 figure 1 shows that TCMR is more significantly differentiated from Quiescence than AMBR. In Cheung 2022, data in the supplement show an AUC of ROC analysis of 0.75 [0.61-0.9) for TCMR, comparable to the overall AUC of 0.78 [0.69-0.87].

6. Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to discriminate acute antibody mediated rejection from quiescence

Yes. The data from both Akalin 2021 and Cheung 2022 show significant ability to differentiate all rejection from quiescence. In Akalin 2021 Figure 1 shows that both TCMR and ABMR are significantly differentiated from quiescence. In Cheung 2022, data in the supplement show an AUC of ROC analysis of 0.79 [0.69-0.89), comparable to the overall AUC of 0.78 [0.69-0.87].

7. Is there sufficient evidence to indicate that in patients without signs and symptoms of rejection, use of molecular diagnostic test (or combination of tests) would preclude the need for kidney biopsy

Yes. The test has a very high NPV. In a surveillance population with a prevalence of 10%, the NPV described in Cheung 2022 is 95% at an AlloMap score of 10.5. This high NPV ensures that negative tests do not need a biopsy.

8. Is there sufficient evidence to indicate that in patients with signs and symptoms of rejection, use of molecular diagnostic test (or combination of tests) would preclude the need for kidney biopsy

Yes. In a for-cause population where the prevalence of rejection has been published at ~25%, the NPV described in Cheung 2022 is 86% at an AlloMap score of 10.5 and reaches an NPV of 93% at a score of 8.0. The high NPV indicates that negative tests have a low probability of rejection and therefore can forego a biopsy.

9. Is there sufficient evidence on the ability of the molecular diagnostic test (or combination of tests) to guide clinical management without a biopsy

Yes, the ability of AlloMap Kidney to inform immune status enables a measure of immune status that informs on the necessity of a biopsy. The performance tables published in Cheung 2022 define the performance characteristics across the range of scores. The report for AlloMap kidney includes the NPV and PPV calculated for the reported score (based on the combined performance of the validation sets in Akalin and Cheung).

9b) If yes for any of the above, what aspect of your clinical management would be influenced by the test result

Biopsies can be avoided based on low AlloMap Kidney scores that indicate adequate immunosuppression to limit the probability of rejection. Additionally, high AlloMap Kidney scores are an indicator of increased immune activity and the possibility of ongoing rejection. This may lead to an effort to optimize immunosuppression or to consideration of other actions such as biopsy if the scores are very high.

10. Would you perform a kidney biopsy if the molecular diagnostic test indicates rejection, but the patient exhibits no signs and symptoms of rejection

If the result is very high, a biopsy may be indicated in the absence of any other information. The data indicate that AlloMap Kidney is a quantitative test that correlates with the degree of immune activity. Therefore, the higher the AlloMap Kidney score, the higher the probability of rejection. Very high scores would warrant a biopsy to investigate. Scores closer to the nominal 10.5% threshold would likely be investigated more closely for immune influences or considered for incremental optimization of immunosuppression in the absence of signs and symptoms of rejection.

13. How confidence are you in the evidence that, for this test, the test results can accurately indicate rejection

Fairly Confident. Two separate multi-center validation datasets both demonstrated the ability of AlloMap Kidney to differentiate from rejection from quiescence. The PPV for AlloMap Kidney is shown in Cheung 2022. In surveillance, the PPV at a score of 10.5 is only 18% in a surveillance population, but the PPV at a score of 15 is 67%. The high score ranges have a high probability of rejection and combined with other assessments this will be a strong indicator of how active the immune system is in respect to the renal allograft.