Virtual Crossmatch (VXM) By The Numbers

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"Manual" VXM

We implemented VXM during November 2019 (through June 2022 as Manual VXM) for our renal transplantation service. We use stringent criteria, considering the VXM as a ***screening assay***, where "***false positives***" are accepted, but "***false negatives***" are not. Class I anti-HLA-A and -B DSA individually >1000 MFI or additively >1200 MFI (where individual MFI >500) are considered positive. Class II anti-HLA-DRB1 and -DQB1 DSA individually >1000 MFI each or additively >1200 MFI (where individual MFI >500), each are considered positive. Anti-HLA-DRB3/4/5 DSA individually >1500 MFI or additively >1750 MFI (where individual MFI >500) are considered positive. Anti-HLA-C and -DPB1 DSA individually >5000 MFI each or additively >6000 MFI (where individual MFI >500), each are considered positive. Anti-HLA-DQA1 and -DPA1 DSA are included if considered positive. For 2 years and 8 months, VXM were performed manually by examining single-antigen bead (SAB) data (One Lambda LABScreen™), using One Lambda FUSION™ and HistoTrac™. (Additional eplet/epitope analyses were performed as needed.) 3427 patient-donor pairs were screened over ~2.7 years (~24 per week) (~2/3 after routine hours) (adding nearly 7.5 hours of additional work each week) (adding nearly 7.5 weeks of additional uncompensated work per year for the directors) with 480 (14%) FCXM, 362 (23%) transplanted (~134 per year). 14% had FCXM performed with 92% concordance to VXM. Thus, 8% of predicted negative FCXM were T+ B+, without elevated DSA. These patients were HIV+, Hep C+, or Hep B+. Discussion with the transplant service would allow for these to be considered for proceeding with transplantation. Occasionally auto-FCXM would be performed for reassurance. There was no hyperacute rejection, and no early post-transplantation rejection.

VXM Using VXMatch™

Beginning July 1, 2022, VXMatch™ (now part of CareDx®) was implemented for better aggregation of the data. DSA MFI criteria remained the same. July 1, 2022 through September 24, 2024, 3886 patient donor pairs have been screened (~2.23 years; ~5 per day, ~34 per week, ~1743 per year) (~2/3 after routine work hours) (adding nearly 7.5 hours of additional work each week, requiring overtime pay to technologists) with 311 transplanted (8%). 446 (11%) had FCXM performed with 91% concordance to VXM. Thus, 9% of predicted negative FCXM were T+ B+, without elevated DSA. These patients were HIV+, Hep C+, or Hep B+. Discussion with the transplant service would allow for these to be considered for proceeding with transplantation. Occasionally auto-FCXM would be performed for reassurance. There was no hyperacute rejection, and no early post-transplantation rejection. (Table 1)

Table 1. Comparison of Manual VXM and VXMatch™

VXM	Total	Per Year	Per Week	Total FCXM Performed (% of VXM)	Total Transplanted (per year) (% of VXM)	VXM FCXM Concordance
Manual	3427	~1269	~24	480 (14%)	362 (~134) (11%)	92%
VXMatch™	3886	~1743	~34	446 (11%)	311 (~139) (8%)	91%

DISCUSSION

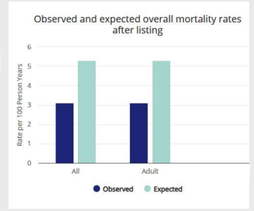
Manually performing VXM is quite time consuming. While outcomes are basically the same, incorporation of VXMatch™ has reduced the time, from as much as an hour per patient performed manually to little as 5 minutes when good data are provided. After extensive training, Laboratory Technologist can become adept at using VXMatch™, as part of their daily and on-call activities. While we cannot obtain the actual reimbursement pay for the VXM Consult. Based on the time requirement to perform, the compensation for the technologists, and the directors' reviews, we lose money. The renal transplant service benefits, and thereby, the patients benefit from our VXM consultation service. Our renal transplant service is nationally ranked, with 5/5 bars for all criteria by the SRTR (Table 2).

Table 2. Percent of Waiting Patients Receiving Transplant During Time Interval

	30 Days	1 Year	2 Years	3 Years
UAMS	17.16	59.17	70.22	74.16
Nationally	5.16	21.37	29.32	35.38

https://www.srtr.org/transplant-centers/

The UAMS Observed Mortality is more than 40% Less Than Other Centers



LIMITATIONS

The major limitation in performing VXM is the information available. Optimal results occur when two-field typing results are available to correspond with the two-field SAB results. Unfortunately, more than 80% of the typing results provided are ambiguous. For example, HLA-A*02:01, *02:03, *02:05, *02:06, *02:07, *02:10, and *02:18 may be in the typing allele string, which are also in the SAB panel. We evaluate all for completeness, rather than only selection HLA-A*02:01 as a reductionist approach. Further, many HLA-DPB1 alleles are not in the SAB panel. We use the UNOS epitopes to address this, to compare with the types in the SAB panel. (Table 3)

Table 3. HLA-DPB1 Epitopes with the Associated Alleles from the SAB Panel

HLA-DPB1 Epitope	Associated Alleles in SAB
55AAE	*01:01, *04:01, *11:01, *13:01, *15:01, *23:01
55DED	*03:01, *06:01, *09:01, *13:01, *14:01, *17:01, *20:01
55DEE	*02:01, *04:02, *10:01, *18:01
55EAE	*05:01, *19:01
84DEAV	*01:01, *03:01, *05:01, *06:01, *09:01, *10:01, *11:01, *13:01, *14:01, *17:01, *19:01, *20:01
84GGPM	*02:01, *02:02, *04:01, *23:01
84VGPM	*15:01, *18:01, *28:01

Another issue is the validity of the data in the SAB assay. Several components are denatured, producing falsely elevated MFI values. We use epitope/eplet analyses to help with determination of likely valid versus invalid results. Further, we consider that the antibody can be spread across multiple beads sharing the same epitope/eplet, thus, actually resulting in a lower MFI value of significance. We use additional aids to help with this:

CREG evaluation; MatchMaker™ (*consider using lower MFI Cut-Offs to evaluate for "Spread" across SAB*); The Epitope/Eplet Registry Website (https://www.epregistry.com.br/index/databases/database/ABC/); The HLA 3D Website (https://www.phla3d.com.br/); HistoCheck (https://www.histocheck.org/histocheck/); HLA-EMMA (https://hla-emma.com/); PIRCHE® (https://www.pirche.com/) VXMatch® and VECTR® (https://caredx.com/virtual-crossmatching-and-epitope-analysis-as-informational-aids-in-the-transplant-decision-making-process-a-review-of-vxmatch-and-vectr/)

CONCLUSIONS

While performing VXM can result in more rapid renal transplantation, complete accuracy cannot be achieved under the current conditions, due to lack of two-field typing results and antibodies to denatured antigens on SAB. Aggregation software with protocol application can allow for Laboratory Technologists to perform VXM as a "screening assay" for which a decision to proceed with FCXM can be made, and/or to proceed with transplantation.