THE ACCEPTABILITY AND APPLICATION OF VIRTUAL CROSSMATCHING IN LIEU OF SEROLOGIC CROSSMATCHING FOR TRANSPLANTATION

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Virtual Crossmatch Workgroup Report Outline

- The Issue
- Working Group Charge
- Background
  - History; - Rationale; - Clinical Impact
- Criteria
- Process
- Personnel
- Decision Algorithm
- Benefits
- Advantages / Disadvantages
- Other Considerations
CFR 493.1278 Standard: Histocompatibility
(f)(2) For renal allotransplantation and combined organ and tissue transplants in which a kidney is to be transplanted, have available results of final crossmatches before the kidney is transplanted.

Concerns of the Transplant Community:
1. This standard is not reflective of evolving clinical practice (ie. Desensitization protocols and use of a virtual crossmatch).
2. This standard puts laboratories at odds with clinicians by dictating clinical practice.
Virtual Crossmatch Workgroup

Workgroup Charge:
Provide input to CLIAC for their consideration in making recommendations to HHS regarding the acceptability and application of virtual crossmatching in lieu of serologic crossmatching for transplantation by providing suggestions for:

- Criteria for determining when a virtual crossmatch is appropriate.
- Guidelines for laboratories performing virtual crossmatching.
Consideration of the Virtual Crossmatch (VXM)

Consider purpose for performing crossmatching (XM) in 2014

- Initially, the purpose of a crossmatch was to prevent hyperacute rejection, which is now very rare.
- When it does occurs, it is predominantly due to NON-HLA antibodies.
- Today, a crossmatch is one parameter for assessing RISK. However, RISK assessment is subjective and may vary by center depending on; the type of transplant, specific donor/recipient pair, program practices and other laboratory findings. A negative crossmatch does NOT confirm the absence of donor-specific antibody nor does it GUARANTEE a successful transplant. Similarly, a Positive crossmatch is not always associated with graft failure.

Scope and Purpose of Virtual Crossmatch (VXM)

- What changes have occurred in the histocompatibility and transplantation fields since the CLIA regulations were published in 1992 that make virtual crossmatching a viable option now?
  - Histocompatibility testing has evolved from cell based assays to molecular typing and solid phase platforms for antibody detection, leading to improved accuracy, sensitivity, specificity.
  - Significant changes have occurred in the clinical practice of transplantation (immunosuppression, desensitization practices) and improvements in anti-rejection therapies have led to improved outcomes and mitigation of risk due to HLA Abs.
THE PRETRANSPLANT CROSSMATCH IS THE MOST IMPORTANT TEST PERFORMED BY THE HLA LABORATORY!
SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION*

RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.
### HOW IT ALL STARTED…

<table>
<thead>
<tr>
<th></th>
<th>REJECTION</th>
<th>NO REJECTION</th>
</tr>
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<tbody>
<tr>
<td>POSITIVE CROSSMATCH</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>NEGATIVE CROSSMATCH</td>
<td>8</td>
<td>187</td>
</tr>
</tbody>
</table>

\[
P = 8.18 \times 10^{-29}
\]

“the ethics of transplanting kidneys without the prior knowledge of the results of the lymphocyte crossmatch test…can reasonably be expected to be questioned.”
Clinical Paradigm (1970s-80s)

Low Risk

Surgical Threshold

T-cell Cytotoxicity XM -ve

Transplant

Patient

High Risk

T-cell Cytotoxicity XM +ve

No Transplant
<table>
<thead>
<tr>
<th>Crossmatch</th>
<th>Rejection</th>
<th>No Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>24</td>
<td>False Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
<td>False Negative</td>
</tr>
</tbody>
</table>

_Patel and Terasaki, NEJM 280:735, 1969_
Assay Improvements

Alternative/Enhanced Cytotoxicity Assays
- Washes
- Anti-globulin

Flow cytometric XM Assay
Kerman et al  Transplantation 68:1855-1858, 1999
The Cell Surface is a Jungle!
Cytotoxicity XM

The evolution and clinical impact of Human Leukocyte Antigen technology

Howard M. Gebel and Robert A. Bray

Current Opinion in Nephrology and Hypertension 2010, 19:598–602

- Less sensitive
- Living cells
- T-cell (class I)
- High frequency of + B-cell XMs NOT due to HLA Abs

Solid Phase Assays

- Most sensitive
- Purified antigens
- Class I and Class II
- Molecular HLA typing
METHODS FOR HLA ANTIBODY EVALUATION

**Antigen Non-Specific**

- Cytotoxicity
  - Standard or NIH
  - Modifications
  - Washes
  - Extended Incubation
  - Antiglobulin

- Flow Cytometry (cells)
  - T cell / B cell
  - Pronase

**Antigen Specific**

- ELISA
  - Yes / No
  - PRA % (I & II)
  - Specificity (I & II)

- Flow Cytometry (beads)
  - PRA % (I and II)
  - Specificity (I & II)

- Multiplex
  - Suspension Arrays
  - Luminex
United Network for Organ Sharing Policies

- Mandate use of molecular methods for HLA typing of deceased donors
- Mandate use of a **solid-phase** assay to identify unacceptable antigens in sensitized candidates

- These policies help ensure that laboratories are employing the most accurate technologies for determining donor HLA types and the most sensitive and specific methods for assessing a candidate’s HLA antibody status
Panel Reactive Antibody (PRA)

A2 specificity:
10/30 cells positive = 33% PRA

Calculated PRA (cPRA)

A2 specificity = 48% of donor pool

A2 and DR4?

- Assessment of HLA alloantibody via reactions with a panel of cells.
- Predominantly Class I
- Assessment of HLA alloantibody via detailed specificity determinations.
- cPRA is a calculated value based on the assigned antigens and their frequency within the donor population.
Enter “unacceptable” antigens into UNOS database.

<table>
<thead>
<tr>
<th>Unacceptable Antigens</th>
<th>Check all A unacceptable antigens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2</td>
<td>3, 9, 10, 11, 19, 23, 24, 25</td>
</tr>
<tr>
<td>26, 66</td>
<td>68, 69, 74, 80, 203, 210, 2403, 2601</td>
</tr>
<tr>
<td>Check all B unacceptable antigens:</td>
<td></td>
</tr>
<tr>
<td>5, 7</td>
<td>8, 12, 13, 14, 15, 16, 17, 18</td>
</tr>
<tr>
<td>21, 22</td>
<td>27, 35, 37, 38, 39, 40, 41, 42</td>
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<tr>
<td>44, 45</td>
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</tr>
<tr>
<td>64, 65, 67</td>
<td>70, 71, 72, 73, 75, 76, 77</td>
</tr>
<tr>
<td>78, 81, 82, 703, 804</td>
<td>1304, 2708, 3901, 3902, 3905</td>
</tr>
<tr>
<td>4005, 5102, 7801, 8201</td>
<td></td>
</tr>
<tr>
<td>Select BW unacceptable antigen:</td>
<td></td>
</tr>
<tr>
<td>4, 6</td>
<td>N/A</td>
</tr>
<tr>
<td>Check all CW unacceptable antigens:</td>
<td></td>
</tr>
<tr>
<td>1, 2</td>
<td>3, 4, 5, 6, 7, 8, 9, 10</td>
</tr>
<tr>
<td>12, 13</td>
<td>14, 15, 16, 17, 18</td>
</tr>
<tr>
<td>Check all DR unacceptable antigens:</td>
<td></td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>4, 5, 6, 7, 8, 9, 10</td>
</tr>
<tr>
<td>11, 12, 13</td>
<td>15, 16, 17, 18, 19, 20</td>
</tr>
<tr>
<td>1404</td>
<td></td>
</tr>
<tr>
<td>Check DR51/52/53 unacceptable antigens:</td>
<td></td>
</tr>
<tr>
<td>51, 52</td>
<td>53</td>
</tr>
<tr>
<td>Check all DQ unacceptable antigens:</td>
<td></td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>4, 5, 6, 7, 8, 9</td>
</tr>
</tbody>
</table>
This patient would be expected to have a positive crossmatch with 60% of the UNOS deceased donors. Donors with “unacceptable antigens” are excluded from kidney match runs.
Solid phase testing and cPRA have increased the rate of transplantation of highly sensitized patients and decreased the rate of organ offer declines due to positive crossmatches.

- **Old**: 7.2%
- **Vol**: 7.3%
- **Man**: 14.1%
- **Man**: 15.8%

### Percentage of Patients Transplanted

- **07/01/2001-12/31/2001**: 0/Not Reported
- **01/01/2002-06/30/2002**: 1-20
- **04/01/2009-09/30/2009**: 21 - 79
- **10/01/2009-03/31/2010**: 80+

### Positive Crossmatches Reported

- **07/01/2001-12/31/2001**: 28,144
- **01/01/2002-06/30/2002**: 27,717
- **04/01/2009-09/30/2009**: 15,579
- **10/01/2009-03/31/2010**: 2,724

Virtual Crossmatch

- What is a Virtual Crossmatch?
- Predicting a Negative “Physical” Crossmatch?
- Predicting a “Compatible” Crossmatch?
- Predicting “Acceptable” Outcomes?

All of the Above?
Working Definition of Virtual Crossmatch

An assessment of immunologic compatibility based on the patient’s alloantibody profile compared to the donor’s histocompatibility antigens.

- Based on well defined antigens and antibodies
- As part of the CMS required agreement with the transplant program, every laboratory must have a policy that defines the process and procedure for performance of a XM – VXM.
- Antibody presence or absence should be confirmed by more than one method and should be reconfirmed on an on-going basis
- Histocompatibility can be defined as encompassing both HLA and non-HLA components.
Can virtual crossmatching be applied to all organ, tissue and/or cellular product transplantation? Yes

- There is no difference in the concept of a virtual crossmatch or physical crossmatch based on organ type.
- How the data from the crossmatch (virtual or physical) are used can differ, depending on the organ.

### Examples:

<table>
<thead>
<tr>
<th></th>
<th>Antibody History</th>
<th>Crossmatch Result</th>
<th>Transplant Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Negative</td>
<td>Negative</td>
<td>YES</td>
</tr>
<tr>
<td>B</td>
<td>Negative</td>
<td>Positive</td>
<td>YES</td>
</tr>
<tr>
<td>C</td>
<td>Positive</td>
<td>Negative</td>
<td>YES/Maybe</td>
</tr>
<tr>
<td>D</td>
<td>Positive</td>
<td>Positive</td>
<td>Maybe ??</td>
</tr>
</tbody>
</table>
What criteria should be considered for determining patient eligibility for a virtual crossmatch?

Consider a virtual crossmatch when there are sufficient data on a patient’s alloantibody status to meet the transplant program-specific criteria. Consider the following:

- When possible and based on transplant urgency and organ type, it is recommended that assessments of alloantibodies be made with more than one specimen.
- Patients must be tested for antibodies against HLA (A, B, C, DRB1, DRB 3, 4, 5, DQB1, DQA1, DPB1, DPA1) and, when relevant, other non-HLA antigens.
- For patients with no identified alloantibodies the frequency of testing may be less than patients with identified alloantibodies. However, each program should determine the definition of a “recent” sample (e.g. <30 days).
- The agreement between the laboratory and the transplant program must describe the circumstances when a prospective physical crossmatch is required.
- When evaluating eligibility, the recipient’s historic and potentially sensitizing events should be considered when available.
- A recipient specimen must be obtained on the day of transplant.
What criteria should be considered when determining donor eligibility for virtual crossmatching?

- Donor typing to include HLA and other histocompatibility antigens to which antibodies have been identified in the potential recipient.
- HLA- DPA1, DPB1, and DQA1 as current example.
Virtual Crossmatching Process

Which methodologies are suitable for obtaining the test results for virtual crossmatching? Are there any methodologies that should be prohibited for this purpose, e.g., methods known to be less sensitive or specific?

- The same technologies that are used for the physical identification of alloantibodies should be applied to virtual assessments.

Are other technological changes anticipated that could influence, or be influenced by adoption of policies that allow for virtual crossmatching? YES

- One example is the potential for computerization of the analysis at the local level.
- UNOS match algorithm as a current example.
Under what circumstances is confirmation of a virtual crossmatch by a serologic crossmatch required?

- Complex (see decision algorithm described on slide #39)
- Must be part of agreement between laboratory and transplant program

Is it necessary to complete the confirmatory crossmatch prior to the transplantation in all of these circumstances? **YES**
Is it possible that the recipient antibody screening, the donor typing, and the virtual crossmatching could all be done in separate locations? **YES**

If yes, what requirements should be in place to ensure the acceptability of test results obtained from another laboratory?

- All testing must be performed in a CLIA-certified and OPTN-approved laboratory
- Results must be available to the person who performs the VXM
- Person performing the VXM must be appropriately qualified, as discussed in following question for personnel requirements
Virtual Crossmatching Process-cont’d

What time limits should not be exceeded between recipient testing and performance of the virtual crossmatching?

- Time limits between donor/recipient testing and the VXM should be specified within the agreement between the laboratory and the transplant program. These may vary based on patients' level of sensitization and history.
- It must be recognized that a virtual crossmatch, not based on a “recent” serum (e.g., within 30 days), may not be an accurate assessment of compatibility. Undocumented pro-inflammatory events and transfusions can increase patient sensitization even among patients considered to be non-sensitized.
- Center-specific protocols should:
  - Include a definition of a “recent” sample
  - Outline procedures for verifying compatibility via a physical crossmatch and/or antibody testing on a sample obtained at the time of transplant.


How is virtual crossmatching compatibility assessed?

Compatibility is assessed by comparing recipient and donor criteria.
Personnel Requirements

What level of personnel should be permitted to perform a virtual crossmatch? Laboratory Director? Technical supervisor? General supervisor? Testing personnel?

- Personnel should meet the CLIA qualifications for a Clinical Consultant of histocompatibility testing as specified in 42 CFR 493.1457.

- A Technical Supervisor or Laboratory Director may meet the Clinical Consultant qualifications and serve in this role. [NOTE: Under CLIA, the responsibilities for a Technical Supervisor or Laboratory Director do not include the interpretation of test results and clinical history that would be required to inform a virtual crossmatch result. Performing the analytic testing of donors and recipients is within responsibilities of a General Supervisor or Testing Personnel, but the interpretation of results, such as would occur with a virtual crossmatch, is covered in the Clinical Consultant responsibilities]

How it Works

Virtual Crossmatch = Acceptable Mismatch

Patient:

A1, A30; B7, B8; DR11, 15; DQ6, 7

Antibodies - DR7, DR9, DR53, DQ2

Potential Donor: complete mismatch

A25, A33; B42, B18; DR8, DR16; DQ4, DQ5

Acceptable Mismatches (AMm)
Relationship between vXM, cPRA and AMm

Donor phenotype = vXM

All HLA + Self HLA Ags - Avoids = AMms

Avoid Ags = cPRA
Role of Flow Cytometry to Define Unacceptable HLA Antigens in Lung Transplant Recipients with HLA-Specific Antibodies

James Z. Appel III, 1, 4 Matthew G. Hartwig, 1 Edward Cantu III, 1 Scott M. Palmer, 2 Nancy L. Reinsmoen, 3 and R. Duane Davis 1

(Transplantation 2006; 81: 1049–1057)

Practical application of the virtual crossmatch


Pretransplant Risk Assessment in Renal Allograft Recipients Using Virtual Crossmatching

D. Bielmann, 1, G. Hönger, 1, D. Lutz, 1, M. J. Mihatsch, 1, J. Steiger, and S. Schaub, 2

Introduction

The presence of preformed donor-specific HLA-antibodies

Ten-Year Experience of Selective Omission of the Pretransplant Crossmatch Test in Deceased Donor Kidney Transplantation

Craig J. Taylor, 1, 5 Vasilis Kosmoliaptsis, 1, 2 Linda D. Sharples, 3 Davide Prezzi, 1, 2 C. Helen Morgan, 1 Timothy Key, 1 Afzal N. Chaudhry, 4 Irum Amin, 2 Menna R. Catloworthy, 4 Andrew J. Butler, 2 Christopher J.E. Watson, 2 and J. Andrew Bradley 2

(Transplantation 2010; 89: 185–193)
Successful Isolated Intestinal Transplantation in Sensitized Recipients With the Use of Virtual Crossmatching


Luminex-based virtual crossmatching for renal transplantation in South Africa

Catherine M Worsley, Elizabeth S Mayne, Melinda S Suchard

A Virtual Crossmatch Protocol Significantly Increases Access of Highly Sensitized Patients to Deceased Donor Kidney Transplantation

Adam W. Bingaman,1,3 Cathi L. Murphey,2 Juan Palma-Vargas,1 and Francis Wright1

Transnational validation of the Australian algorithm for virtual crossmatch allocation in kidney paired donation

Georg A. Böhmig, Samantha Fidler, Frank T. Christiansen, Gottfried Fischer, Paolo Ferrari


(Transplantation 2008;86: 1864–1868)

Human Immunology 74 (2013) 500–505
How should results be documented and reported? For example, should the report to the transplant surgeon indicate that the crossmatch result is based on a virtual assessment?

- Request for a virtual crossmatch should be initiated by the transplant program.
  - Should follow same process as any other laboratory test.
  - Should indicate which donor:recipient pair.
  - One request per pair.
- Report should indicate that a virtual crossmatch was performed.
- Report may include both virtual and physical crossmatch results if available.
- A report should be submitted to the potential recipient’s permanent medical record, independent of whether a transplant occurs, as documentation that a specific candidate was considered for transplant.
Which donor and patient test results should be required in a virtual crossmatch decision algorithm?

- Patients and donors should have sufficient level of HLA typing to permit accurate virtual crossmatch assessment. For broadly sensitized patients, this may include typing at all major HLA loci: HLA-A,B,C, DRB1, DRB3-5, DQA, DQB1, DPA, and DPB1.
- Results of antibody identification performed using at least one solid phase immunoassay on at least two patient sera. (This provides confirmation of potential donor-specific antibodies and is a safeguard against possible sample switches).

What factors should be considered in developing decision algorithms for virtual crossmatching?

- The acceptable level of risk at the transplant center – may be patient specific.
- Patient risk factors such as, previous transplants, sensitization history, breadth of sensitization and relative antibody strength.
- Acceptable time frames for sera used for virtual crossmatches – may be patient specific (eg: <30 days for sensitized patients and >30 days for unsensitized patients).
- Procedures for ensuring compatibility at the time of transplant when non-recent sera are used for the virtual crossmatch.
**Decision Algorithms – Selected Examples**

<table>
<thead>
<tr>
<th>Antibody Profile</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>1</td>
</tr>
<tr>
<td>No AB</td>
<td>Abs present</td>
</tr>
<tr>
<td>None</td>
<td>Well defined</td>
</tr>
<tr>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>None</td>
<td>No recent</td>
</tr>
<tr>
<td>Recent</td>
<td>Recent</td>
</tr>
</tbody>
</table>

**Virtual Crossmatch Eligible**

- **YES**
  - Perform Concurrent or Retrospective Physical Crossmatch with day-of-transplant sample
- **NO**
  - Prospective Physical XM Required

Adapted from S. Leffell
How should “indeterminate” results from virtual crossmatches be managed?

- Policy should be determined by each transplant program and included in the agreement between the laboratory and that program
- Could be grounds to require a physical XM

When should the virtual crossmatch results/interpretation be verified by a second individual?

- While test results should be reviewed and verified by more than one individual who meets the appropriate CLIA qualifications, the VXM is an interpretation of existing results by a Clinical Consultant. Requiring a review by two individuals is generally not possible since virtual crossmatching often occurs in the middle of the night and most laboratories have only one qualified as a Clinical Consultant.
What are the potential benefits of virtual crossmatches for patients?

- Less time needed for evaluation of compatibility (particularly with thoracic transplant patients); results in more efficient use of the system
- Reduced cold ischemia time
- Facilitates matching over larger geographic area, renal paired donations, and the transplantation of more highly sensitized patients
- Can result in improved access for sensitized patients
- Increased sensitivity and specificity of testing can lead to a better matched donor/recipient
- More specific than serologic crossmatch-(includes patient history, etc)
- Less likely to deny access for a false positive physical crossmatch
- Reduced cost
- Does not preclude the performance of a physical XM; however, this may be completed concurrent with or after transplantation
- Aids in risk assessment for patient desensitization needs
Potential Benefits—cont’d

Laboratories?
- Increased efficiency, which allows for more focus on patients with problems and results in cost savings
- Decreased on-call time expenditure by testing personnel
- Allows for better coordination and communication with transplant programs
- Improved quality management with better patient and transplant program satisfaction

Transplant programs?
- Reduced ischemia time
- Improved access to transplantation for immunologically and geographically disadvantaged candidates, which results in improved transplant physician and patient satisfaction
- Fewer unexpectedly positive physical crossmatches leads to more efficient use of transplant personnel
- Improved risk assessment for rejection
- Allows for optimized immunosuppression and desensitization protocols
- Flexibility in managing transplant related logistics (i.e. OR schedules)
- Cost savings

Others?
- Benefits donor families in that there is a greater possibility that donated organs will be used
- Cost savings to payers
Potential Disadvantages of Virtual Crossmatches

What are the potential disadvantages of virtual crossmatches to:

patients?
- Based on the program’s criteria for crossmatches, there is potential to deny use of a donor organ that could be successfully transplanted
- Requires patient to receive and understand more complicated information
- Negative crossmatch (physical or virtual) does not guarantee compatibility

laboratories?
- Potentially more difficult for staff to maintain competency in performing physical crossmatches when they are done less frequently
- Increased unreimbursed interpretation time
- Requires more coordination with transplant program

transplant programs?
- Program staff have to learn a new interpretive vocabulary
- Additional time and work to ensure that patients understand their risk and get all the information on time

others?
- No reimbursement for time/effort of professional rendering a virtual crossmatch
What other factors should be considered?

In what ways does virtual crossmatching provide “equivalent quality” to serologic crossmatching? How is “equivalent quality” defined and verified for this process?

- Quality is not equivalent in all scenarios
- Equivalence can be stratified by degree of sensitization
  - Unsensitized vs highly sensitized (see slide #39)
- VXM is based on well-defined antibody specificity assessments
- Serologic XM gives total reactivity against donor lymphocytes which may not be HLA specific – ie; false positive results –may be clinically irrelevant.

Is additional guidance needed for laboratories that perform virtual crossmatching?

YES.

- Confirmation of recipient antibody specificity for the VXM by more than one method is recommended
  - May use multiple solid-phase testing platforms or surrogate physical crossmatches
- Specificity should be reconfirmed on an on-going basis
  - Time frames for defining a “recent” sample should be based on patient sensitization history and transplant center practices
- A serum sample must be collected and stored on day of transplant
  - Post transplant donor specific antibody assessments
  - Medical/Legal issues
Evolving Clinical Paradigm (2014 →)

Low Risk

- Patient
  - T and B cell
  - CDC-XM & solid-phase -ve &
    - or
  - Flow-XM &
    - or
  - solid-phase –ve
  - or
  - Solid-phase –ve
  - or
  - reliable history
  - VXM -

Transplant

Surgical Threshold

High Risk

- Patient
  - T and B cell
  - CDC-XM +ve & Solid Phase +ve
    - or
  - Flow-XM +
    - or
  - Level of Solid Phase +ve
  - or
  - VXM +

Contraindicated
Questions?