

# Virtual Crossmatch Workgroup Report

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

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# Virtual Crossmatch Workgroup Report Outline

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- **The Issue**
- **Working Group Charge**
- **Background**
  - History; - Rationale; - Clinical Impact
- **Criteria**
- **Process**
- **Personnel**
- **Decision Algorithm**
- **Benefits**
- **Advantages / Disadvantages**
- **Other Considerations**

# The Issue

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## 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

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## 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)

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## 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 occur, 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.

# Original PARADIGM

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**THE PRETRANSPLANT CROSSMATCH IS  
THE MOST IMPORTANT TEST  
PERFORMED BY THE HLA LABORATORY!**

# The New England Journal of Medicine

Copyright, 1969, by the Massachusetts Medical Society

Volume 280

APRIL 3, 1969

Number 14

## 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...

9

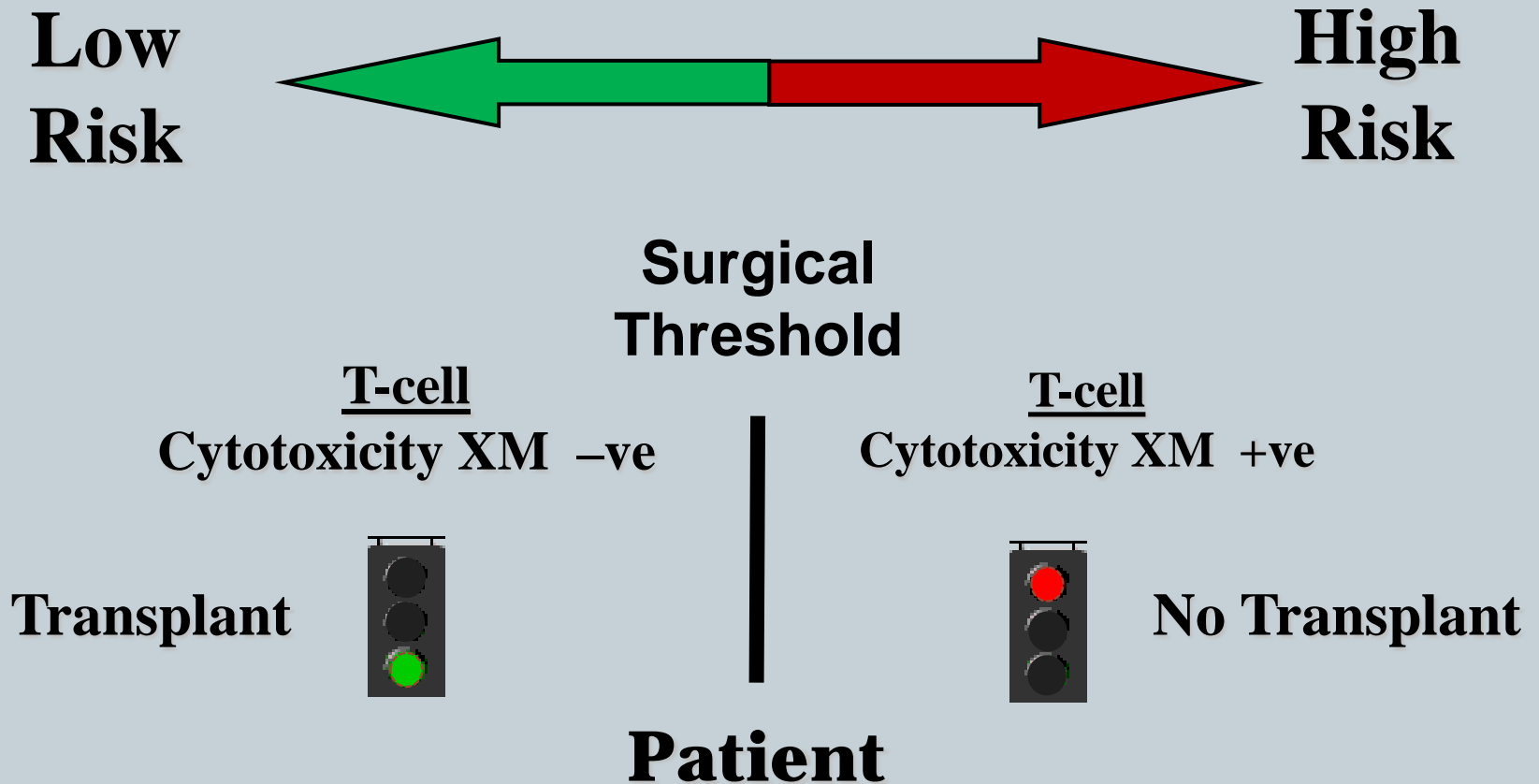
	<u>REJECTION</u>	<u>NO REJECTION</u>
POSITIVE CROSSMATCH	24	6
NEGATIVE CROSSMATCH	8	187

$$P = 8.18 \times 10^{-29}$$

“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)

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# HOW IT ALL STARTED...

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REJECTION

NO REJECTION

**POSITIVE CROSSMATCH**

**24**

**False Positive**

**6**

**NEGATIVE CROSSMATCH**

**8**

**False Negative 187**

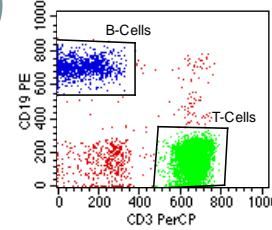
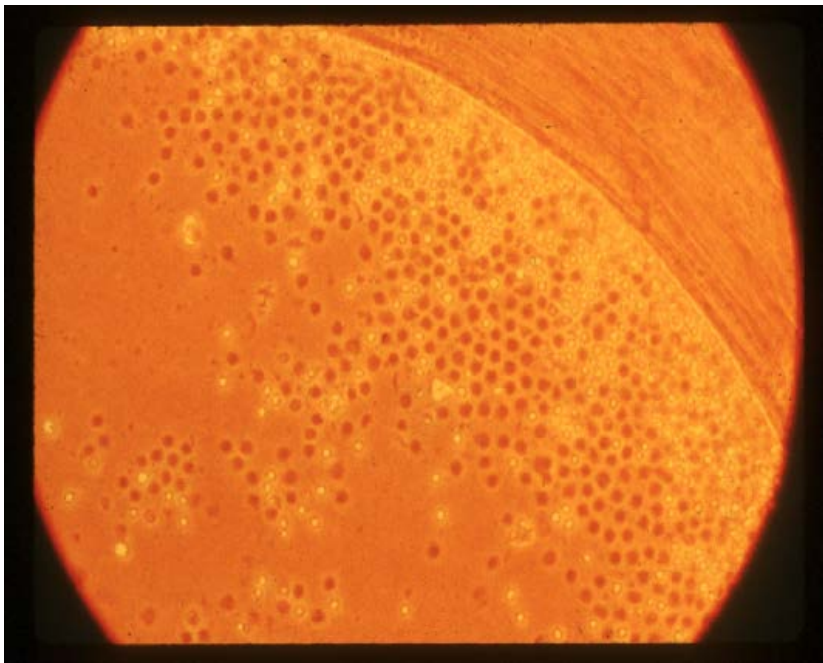
*PATEL AND TERASAKI, NEJM 280:735, 1969*

# Assay Improvements

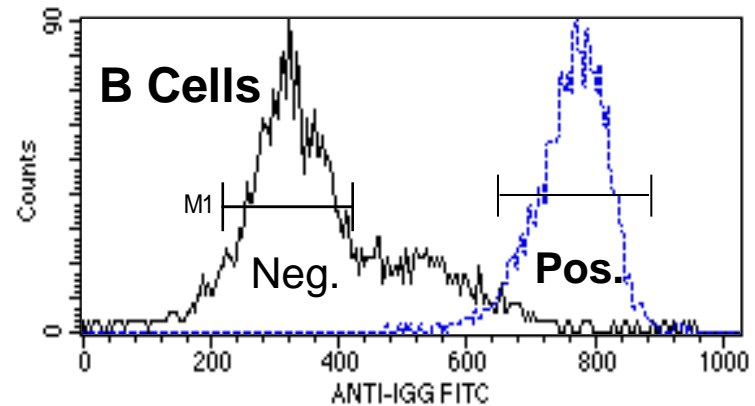
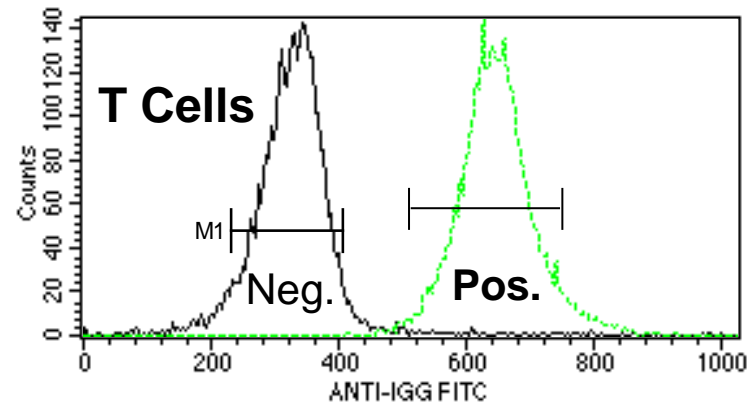
12

## Alternative/Enhanced Cytotoxicity Assays

- Washes
- Anti-globulin

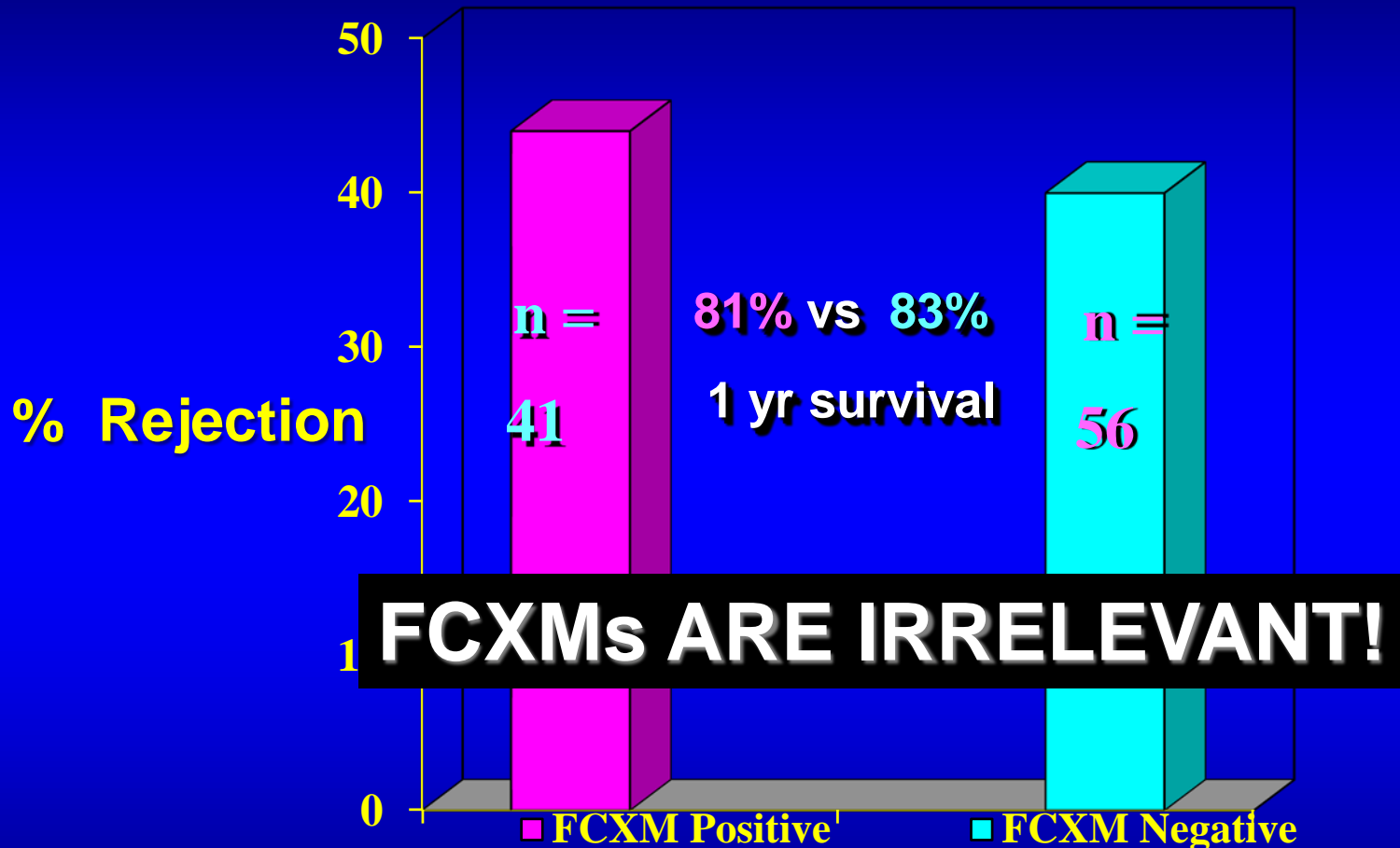


## Flow cytometric XM Assay



# IgG FCXM:Renal Allograft Study

Frequency of rejection in a single center



*Kerman et al Transplantation 68:1855-1858, 1999*

# The Cell Surface is a Jungle!





# 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

## Solid Phase Assays

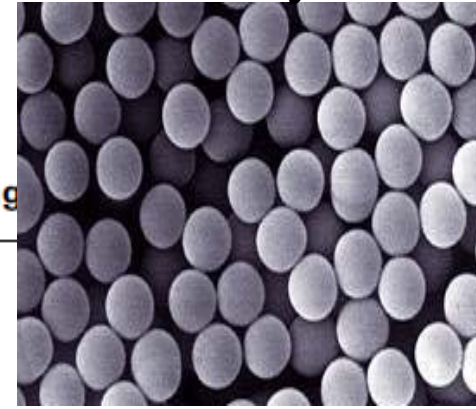
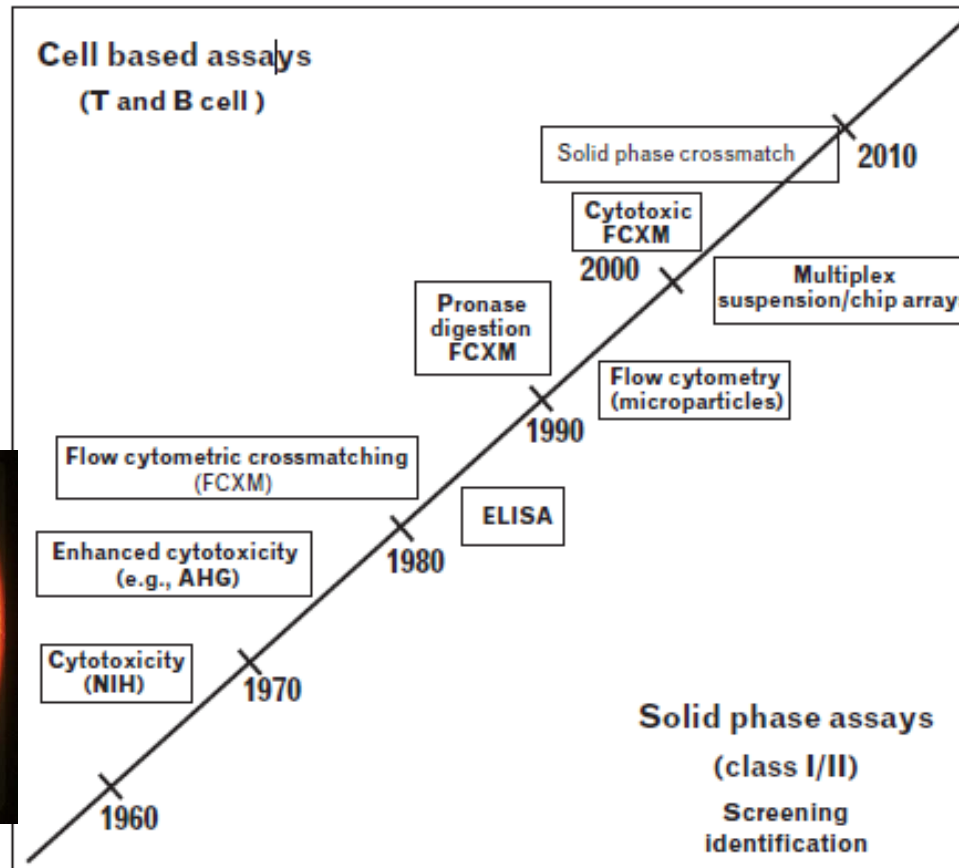
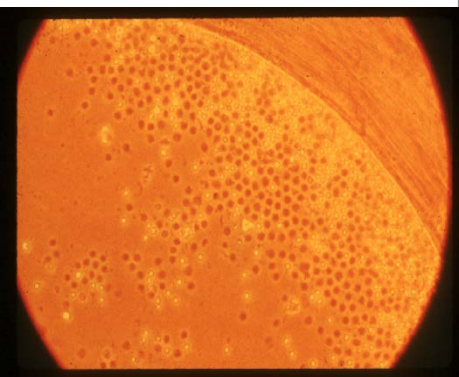


Figure 1 Evolution of human leukocyte antigen antibody testing



- Most sensitive
- Purified antigens
- Class I and Class II
- Molecular HLA typing

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



Cytotoxicity XM

# METHODS FOR HLA ANTIBODY EVALUATION

## Antigen Non-Specific

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### Cytotoxicity

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

### Flow Cytometry (cells)

- T cell / B cell
- Pronase

## Antigen Specific

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### ELISA

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

### Flow Cytometry (beads)

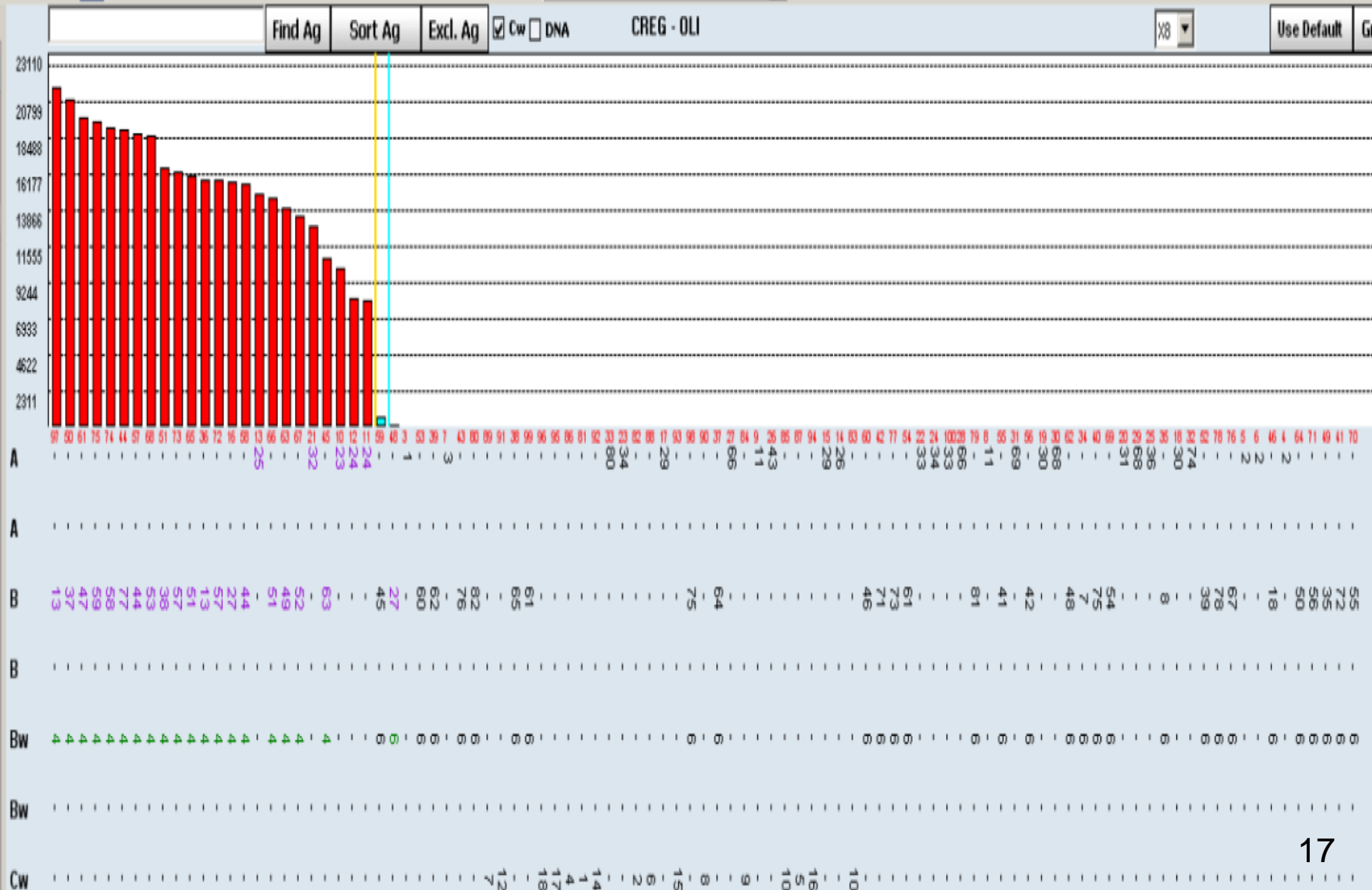
- PRA % (I and II)
- Specificity (I & II)

### Multiplex

- Suspension Arrays
  - Luminex



# Example - Single Antigen Bead Result



# United Network for Organ Sharing Policies

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- 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*

# UNOS Policies – cont'd

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## Panel Reactive Antibody (PRA)

A2 specificity:

10/30 cells positive = 33% PRA

VS

## 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.

# UNET – Calculated PRA

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Enter “unacceptable” antigens into UNOS database.

**Active List**

- Search
- Add
- Feedback
- Justification Forms
- Reported Deaths
- Removal History**
- Lab Data
- Acceptance Criteria
- Organ Offers
- Reports
- Review Board

**Unacceptable Antigens**  
One or more unacceptable antigens must be indicated in order to receive PRA Points. The unacceptable antigens should be able to support the PRA.

Check all A unacceptable antigens:

<input type="checkbox"/> 1	<input checked="" type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 9	<input type="checkbox"/> 10	<input type="checkbox"/> 11	<input type="checkbox"/> 19	<input type="checkbox"/> 23	<input type="checkbox"/> 24	<input type="checkbox"/> 25
<input type="checkbox"/> 26	<input type="checkbox"/> 27	<input type="checkbox"/> 29	<input type="checkbox"/> 30	<input type="checkbox"/> 31	<input type="checkbox"/> 32	<input type="checkbox"/> 33	<input type="checkbox"/> 34	<input type="checkbox"/> 36	<input type="checkbox"/> 43
<input type="checkbox"/> 66	<input type="checkbox"/> 68	<input type="checkbox"/> 69	<input type="checkbox"/> 74	<input type="checkbox"/> 80	<input type="checkbox"/> 203	<input type="checkbox"/> 210	<input type="checkbox"/> 2403	<input type="checkbox"/> 6601	<input type="checkbox"/> 6602

Check all B unacceptable antigens:

<input type="checkbox"/> 5	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 12	<input type="checkbox"/> 13	<input type="checkbox"/> 14	<input type="checkbox"/> 15	<input type="checkbox"/> 16	<input type="checkbox"/> 17	<input type="checkbox"/> 18
<input type="checkbox"/> 21	<input type="checkbox"/> 22	<input type="checkbox"/> 27	<input type="checkbox"/> 35	<input type="checkbox"/> 37	<input type="checkbox"/> 38	<input type="checkbox"/> 39	<input type="checkbox"/> 40	<input type="checkbox"/> 41	<input type="checkbox"/> 42
<input type="checkbox"/> 44	<input type="checkbox"/> 45	<input type="checkbox"/> 46	<input type="checkbox"/> 47	<input type="checkbox"/> 48	<input type="checkbox"/> 49	<input type="checkbox"/> 50	<input type="checkbox"/> 51	<input type="checkbox"/> 52	<input type="checkbox"/> 53
<input type="checkbox"/> 54	<input type="checkbox"/> 55	<input type="checkbox"/> 56	<input type="checkbox"/> 57	<input type="checkbox"/> 58	<input type="checkbox"/> 59	<input type="checkbox"/> 60	<input type="checkbox"/> 61	<input type="checkbox"/> 62	<input type="checkbox"/> 63
<input type="checkbox"/> 64	<input type="checkbox"/> 65	<input type="checkbox"/> 67	<input type="checkbox"/> 70	<input type="checkbox"/> 71	<input type="checkbox"/> 72	<input type="checkbox"/> 73	<input type="checkbox"/> 75	<input type="checkbox"/> 76	<input type="checkbox"/> 77
<input type="checkbox"/> 78	<input type="checkbox"/> 81	<input type="checkbox"/> 82	<input type="checkbox"/> 703	<input type="checkbox"/> 804	<input type="checkbox"/> 1304	<input type="checkbox"/> 2708	<input type="checkbox"/> 3901	<input type="checkbox"/> 3902	<input type="checkbox"/> 3905
<input type="checkbox"/> 4005	<input type="checkbox"/> 5102	<input type="checkbox"/> 5103	<input type="checkbox"/> 7801	<input type="checkbox"/> 8201					

Select BW unacceptable antigen:

4     6     N/A

Check all CW unacceptable antigens:

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
<input type="checkbox"/> 12	<input type="checkbox"/> 13	<input type="checkbox"/> 14	<input type="checkbox"/> 15	<input type="checkbox"/> 16	<input type="checkbox"/> 17	<input type="checkbox"/> 18			

Check all DR unacceptable antigens:

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input checked="" type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
<input type="checkbox"/> 11	<input type="checkbox"/> 12	<input type="checkbox"/> 13	<input type="checkbox"/> 14	<input type="checkbox"/> 15	<input type="checkbox"/> 16	<input type="checkbox"/> 17	<input type="checkbox"/> 18	<input type="checkbox"/> 103	<input type="checkbox"/> 1403
<input type="checkbox"/> 1404									

Check DR51/52/53 unacceptable antigens:

<input type="checkbox"/> 51	<input type="checkbox"/> 52	<input type="checkbox"/> 53
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Check all DQ unacceptable antigens:

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9
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# cPRA

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## Clinical Information

### Active List

Search  
Add  
Feedback  
Justification Forms  
Reported Deaths

### Removal History

### Lab Data

### Acceptance Criteria

### Organ Offers

### Reports

### Review Board

ABO:	O								
Height:	5 ft 9 in / 175.26 cm								
Weight:	213 lbs / 96.6151 kg								
HLA:	A: 1	A: 11	B: 35	B: 44	BW4: P	BW6: P	CW: 4	CW: 6	
	DR: 7	DR: 13	DR51: N	DR52: P	DR53: P	DQ: 2	DQ: 6		
Peak PRA:	60				Calculated PRA (CPRA):				
Current PRA:	60				60				
Choose PRA for allocation scoring:	Peak				NOTE: The unacceptable antigens entered are used to determine the CPRA score. This score is used to screen candidates from matches for donors with antigens listed as unacceptable. The CPRA is for information only. CPRA is not used in organ allocation at this time.				
Measured (actual urinary collection) creatinine clearance level less than or equal to 20ml/min.?	NO								
Calculated GFR (Cockcroft-Gault or other reliable formula) less than or equal to 20 ml/min.?	NO								
Is candidate currently on dialysis?	YES								
Initial Dialysis Date:	10/16/2005								

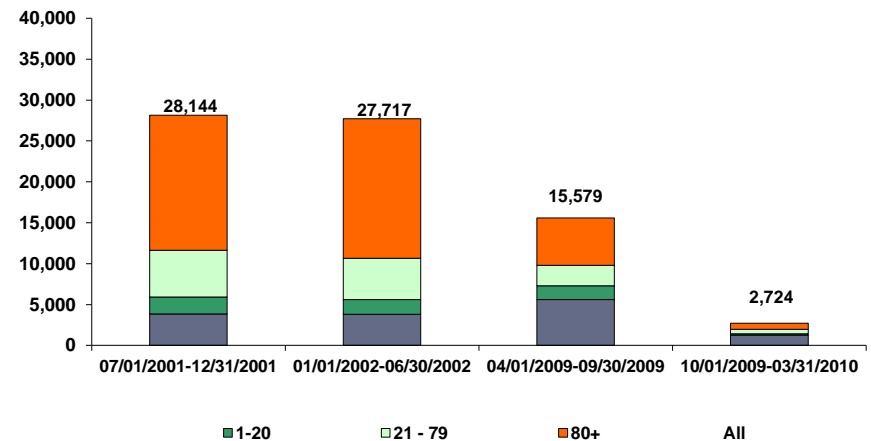
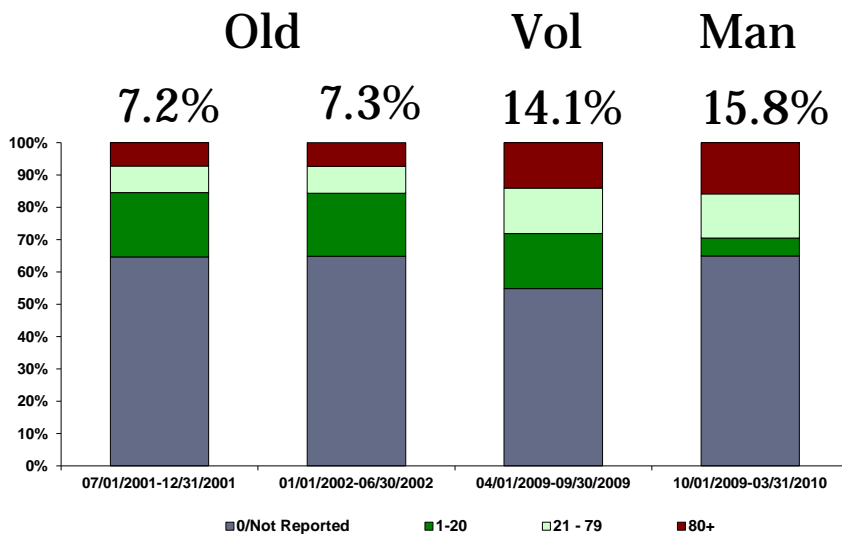
This patient would be expected to have a positive crossmatch with **60%** of the UNOS deceased donors.

Donors with “unacceptable antigens” are excluded from kidney match runs.

# Impact of Solid Phase Testing and cPRA

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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.



Percentage of Patients Transplanted

Positive Crossmatches Reported

# Virtual Crossmatch

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- **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

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*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.



# Criteria for Determining when Virtual Crossmatches are Appropriate

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- **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.

<b>Examples:</b>	<u>Antibody History</u>	<u>Crossmatch Result</u>	<u>Transplant Decision</u>
A	Negative	Negative	YES
B	Negative	Positive	YES
C	Positive	Negative	YES/Maybe
D	Positive	Positive	Maybe ??

# Criteria-cont'd

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## 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.

# Criteria-cont'd

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## **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

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**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.

# Virtual Crossmatching Process-cont'd

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**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****

# Virtual Crossmatching Process-cont'd

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**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

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## 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.

➤ Locke JE, et al Proinflammatory events are associated with significant increases in breadth and strength of HLA-specific antibody. *Am J Transplant.* 2009;9:2136

➤ Leffell MS, et al. Red blood cell transfusion and the risk of allosensitization in patients awaiting primary kidney transplantation. *Transplantation.* 2014; 97: 52

# Virtual Crossmatching Process-cont'd

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## How is virtual crossmatching compatibility assessed?

Compatibility is assessed by comparing recipient and donor criteria.



# Personnel Requirements

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**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**

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**Patient:**

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

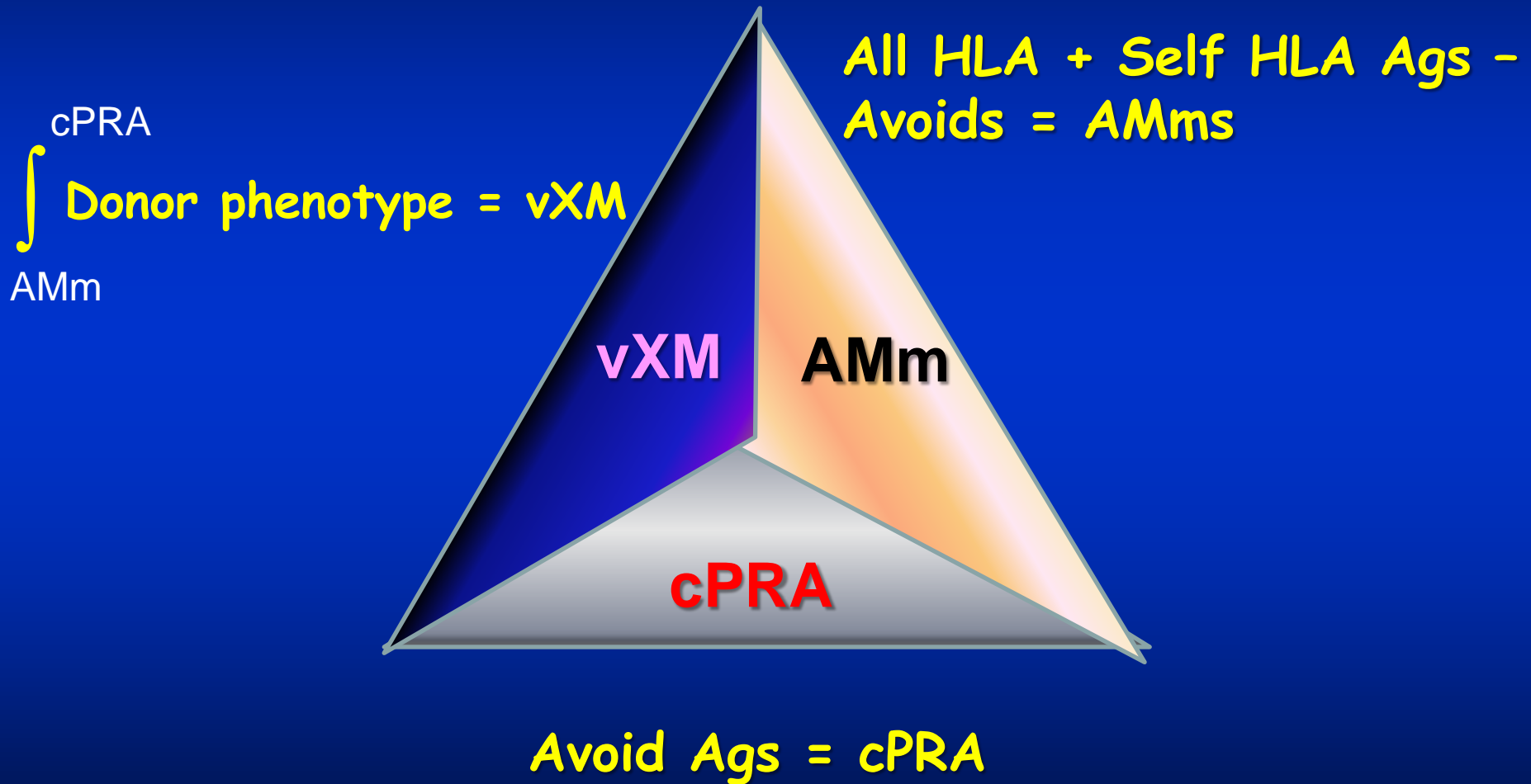
**Antibodies - DR7, DR9, DR53, DQ2**

**Potential Donor: complete mismatch**

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

**Acceptable Mismatches (AMm)**

# Relationship between vXM, cPRA and AMm



# Role of Flow Cytometry to Define Unacceptable HLA Antigenes in Lung Transplant Recipients with HLA-Specific Antibodies

(*Transplantation* 2006;81: 1049–1057)

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

*Pediatr Transplantation* 2007; 11: 650–654

Copyright © 2007 Blackwell Munksgaard

Pediatric Transplantation

DOI: 10.1111/j.1399-3046.2007.00746.x

## Practical application of the virtual crossmatch

Zangwill S, Ellis T, Stendahl G, Zahn A, Berger S, Tweddell J. Practical application of the virtual crossmatch. *Pediatr Transplantation* 2007; 11: 650–654. © 2007 Blackwell Munksgaard

*American Journal of Transplantation* 2007; 7: 626–632  
Blackwell Munksgaard

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Journal compilation © 2007 The American Society of  
Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/j.1600-6143.2007.01667.x

## Pretransplant Risk Assessment in Renal Allograft Recipients Using Virtual Crossmatching

D. Biemann<sup>a,1</sup>, G. Hönger<sup>a,1</sup>, D. Lutz<sup>a</sup>,  
M. J. Mihatsch<sup>b</sup>, J. Steiger<sup>a</sup> and S. Schaub<sup>a,\*</sup>

### 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 (*Transplantation* 2010;89: 185–193)

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

# Successful Isolated Intestinal Transplantation in Sensitized Recipients With the Use of Virtual Crossmatching

*American Journal of Transplantation* 2012; 12: S33–S42

J. S. Hawksworth, S. Rosen-Bronson, E. Island, R. Girlanda, J. F. Guerra, C. Valdicenza, K. Kishiyama, K. D. Christensen, S. Kozlowski, S. Kaufman, C. Little, K. Shetty, J. Laurin, R. Satoskar, B. Kallakury, T. M. Fishbein and C. S. Matsumoto\*

tation; MCS, median channel shift; MFI, mean fluorescence intensity; NOD, nucleotide-binding oligomerization domain-containing protein 2; PRA, panel reactive antibody (%); PTLD, posttransplant lymphoproliferative disorder; SGS, short gut syndrome; TPN, total parenteral nutrition; VXM, virtual crossmatch.

Received 16 February 2012. revised 12 July 2012 and

## Luminex-based virtual crossmatching for renal transplantation in South Africa

Catherine M Worsley, Elizabeth S Mayne, Melinda S Suchard

*S Afr Med J* 2012;102:40–43.

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

*(Transplantation* 2008;86: 1864–1868)

Adam W. Bingaman,<sup>1,3</sup> Cathi L. Murphey,<sup>2</sup> Juan Palma-Vargas,<sup>1</sup> and Francis Wright<sup>1</sup>

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

Georg A. Böhmig<sup>a</sup>, Samantha Fidler<sup>b,c</sup>, Frank T. Christiansen<sup>b,c</sup>, Gottfried Fischer<sup>d</sup>, Paolo Ferrari<sup>e,f,\*</sup>

*Human Immunology* 74 (2013) 500–505

# Virtual Crossmatching Process-cont'd

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**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.

# Decision Algorithms

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## **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

## Patients

Antibody Profile	1	2	3
- <b>History</b>	No AB	Abs present	Abs present
- <b>Specificity</b>	None	Well defined	Not well defined
- <b>Current DSAs</b>	None	No	Yes / Unclear
- <b>Historic DSAs</b>	None	No	Yes / No ?
- <b>Sensitizing events</b>	None	No recent	Possible recent
- <b>Last sample</b> (eg; <30 days)	Recent	Recent	Recent/not recent
<b>Virtual Crossmatch Eligible</b>	<b>YES</b> ↓	<b>YES</b> ↓	<b>NO</b> ↓
	<div style="border: 1px solid black; padding: 10px; width: fit-content; margin: 0 auto;"> <b>Perform Concurrent or Retrospective Physical Crossmatch with day-of-transplant sample</b> </div>		<div style="border: 1px solid black; padding: 10px; width: fit-content; margin: 0 auto;"> <b>Prospective Physical XM Required</b> </div>



# Decision Algorithms

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## 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.

# Potential Benefits of Virtual Crossmatches

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## 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

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## 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

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**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?

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

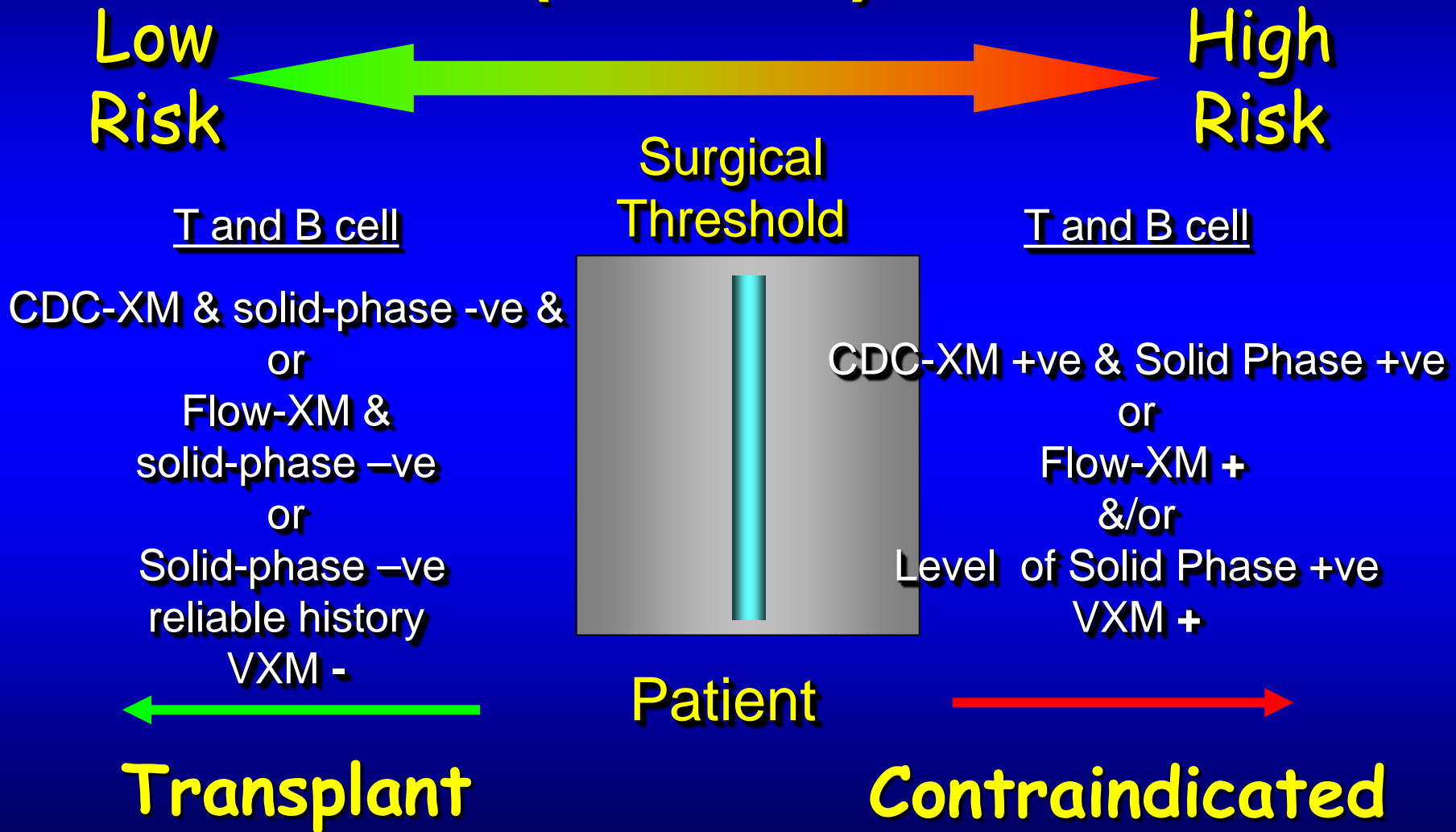
- Quality is not equivalent in all scenarios
- Equivalence can be stratified by degree of sensitization
  - Unsensitized vs highly sensitized (see slide #39)
- VXM is based on well-defined antibody specificity assessments
- Serologic XM gives total reactivity against donor lymphocytes which **may not** 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 →)



# Questions?

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