Renal Transplant Pathology

Summary of Banff 2022

The 30th anniversary of the first Banff Classification

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12 March 2024- Nephrology Webinar- Isfahan University of Medical Sciences

The Banff Schema was first developed by a group of pathologists, nephrologists, and transplant surgeons at a meeting in Banff Canada August 2-4, 1991.

It has continued to evolve through meetings every two years and has become the worldwide standard for interpretation of transplant biopsies.

Courtesy of Dr. Solez


XVIth Banff Meeting Allograft
pathology, Joint meeting with the
Canadian Society of Transplantation
Banff Alberta Canada
19th-23rd September 2022
Lake Louise (Sunrise)

To mark the 30th anniversary of the first Banff Classification (1991), premeeting discussions were held on the past, present, and future of the Banff Classification.

premeeting discussions

"The banff classification is changing too often"

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
	1991	1993	1995	1997	1999	2001	2003	2005	2007	2009	2011	2013	2015	2017	2019
Change	n/a		x	x		x		x	x			x	x	x	x

American Journal of Transplantation 24 (2024) 338–349

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Meeting report

The Banff 2022 Kidney Meeting Report: Reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics

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This report is a summary of the meeting highlights that were most important in terms of their effect on the Classification, including discussions around :

- **Microvascular inflammation:**

Inflammation within peritubular capillaries (PTCs) together with glomerulitis (g) constitutes MVI as a feature of Active AMR or Chronic Active AMR.

Updates of 2019 Banff classification

- Category 1: Normal biopsy or nonspecific changes
- Category 2: Antibody-mediated changes

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury
2. Evidence of current/recent antibody interaction with vascular endothelium
3. Serologic evidence of circulating donor-specific antibodies(DSA to HLA or other antigens).

C4d staining or expression of validated transcripts/ classifiers as noted above in criterion 2 may substitute for DSA

TABLE 4 Updates of 2019 Banff classification for ABMR, borderline changes, TCMR, and polyomavirus nephropathy. All updates in boldface type[a]

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

Active ABMR; all 3 criteria must be met for diagnosis

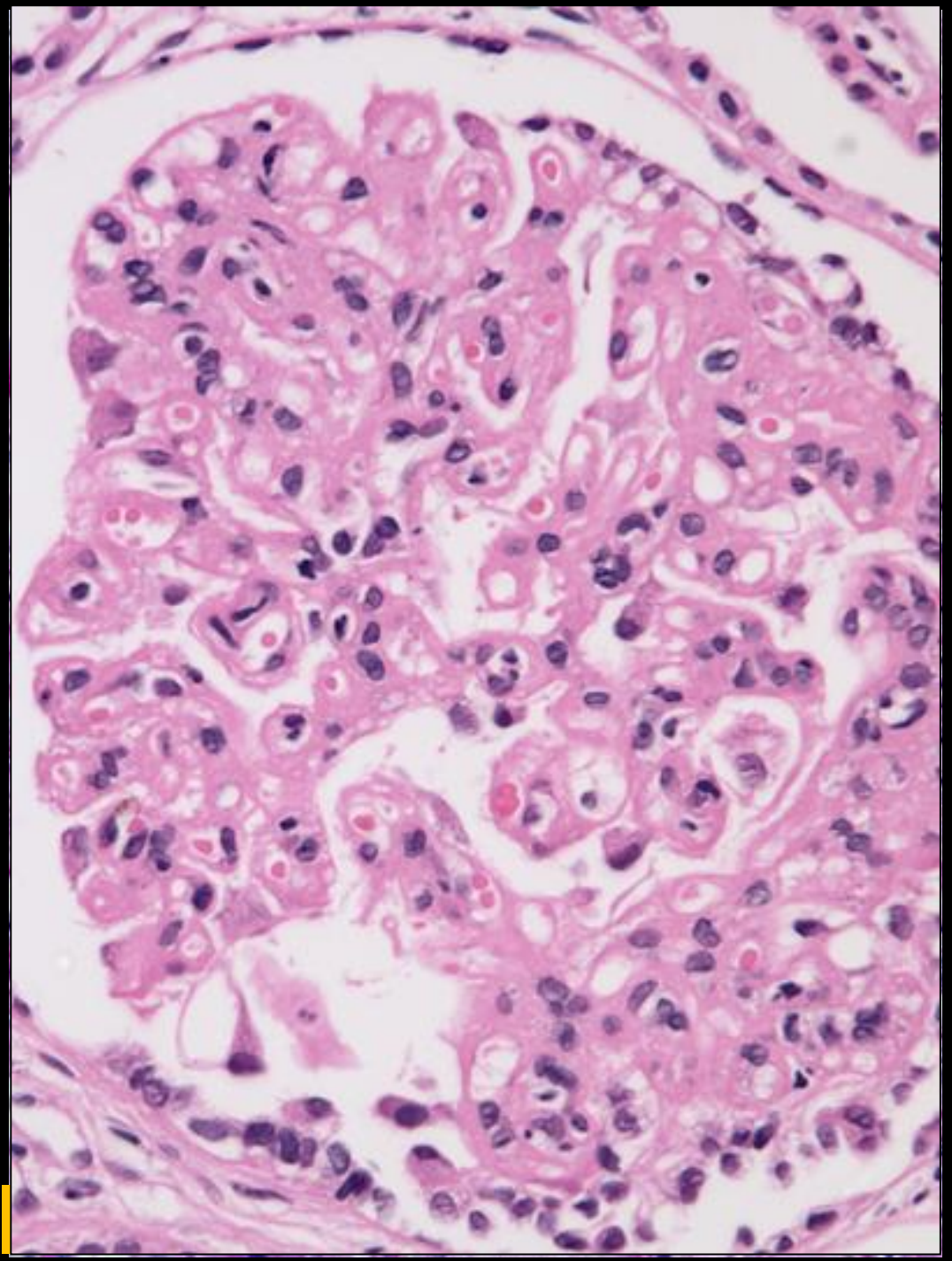
1. Histologic evidence of acute tissue injury, including 1 or more of the following:
   - Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
   - Intimal or transmural arteritis (v > 0)[b]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause

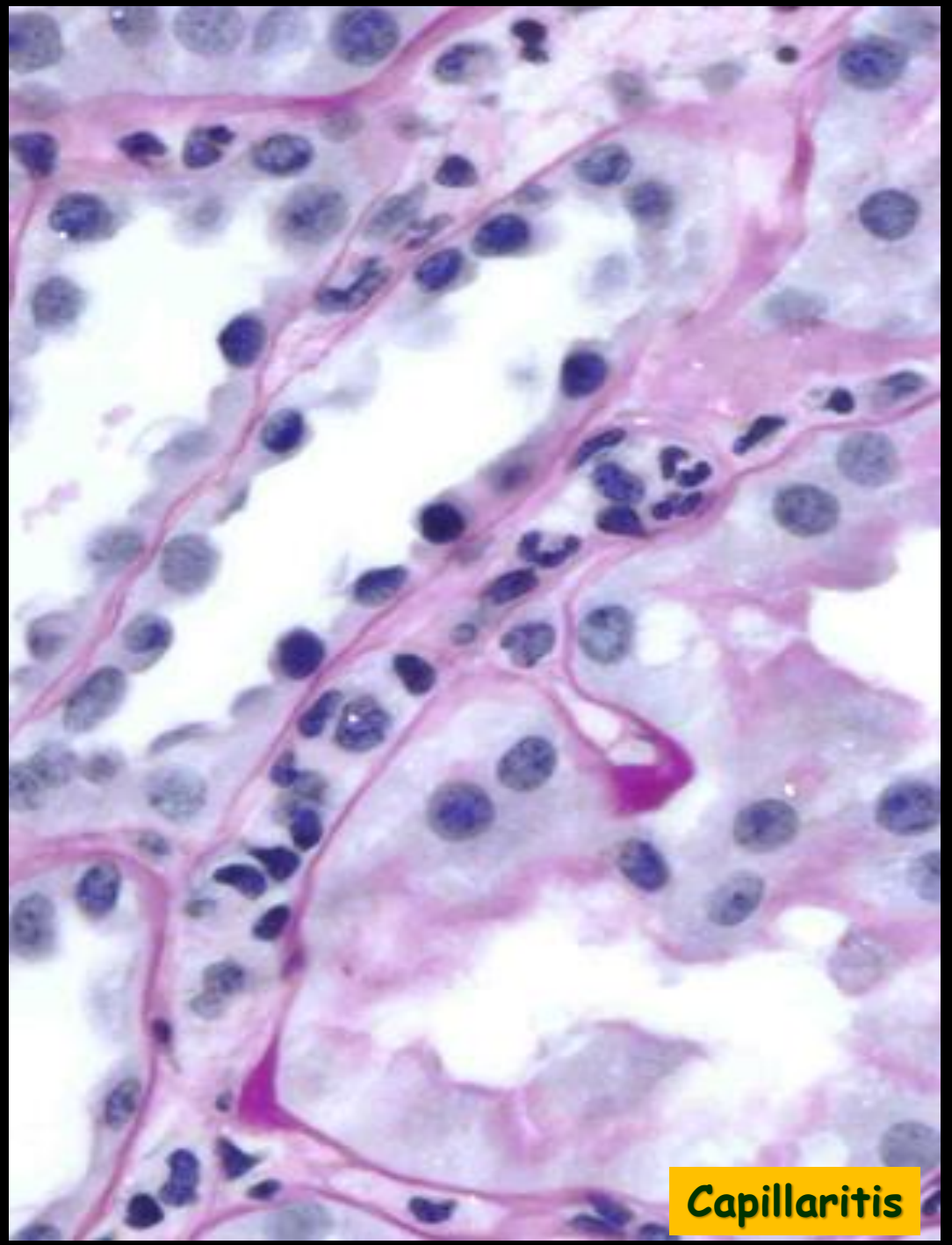
Quantitative criteria for glomerulitis: g score	
g0	No glomerulitis
g1	Glomerulitis in <25% of glomeruli
g2	Segmental or global glomerulitis in 25–75% of glomeruli
g3	Glomerulitis in >75% of glomeruli
Quantitative criteria for peritubular capillaritis: ptc score	
ptc0	At least one leukocyte in <10% of cortical PTCs and/or maximum number of leukocytes <3
ptc1	At least one leukocyte cell in ≥10% of cortical PTCs with three or four leukocytes in most severely involved PTC
ptc2	At least one leukocyte in ≥10% of cortical PTCs with five to 10 leukocytes in most severely involved PTC
ptc3	At least one leukocyte in ≥10% of cortical PTCs with >10 leukocytes in most severely involved PTC

2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:

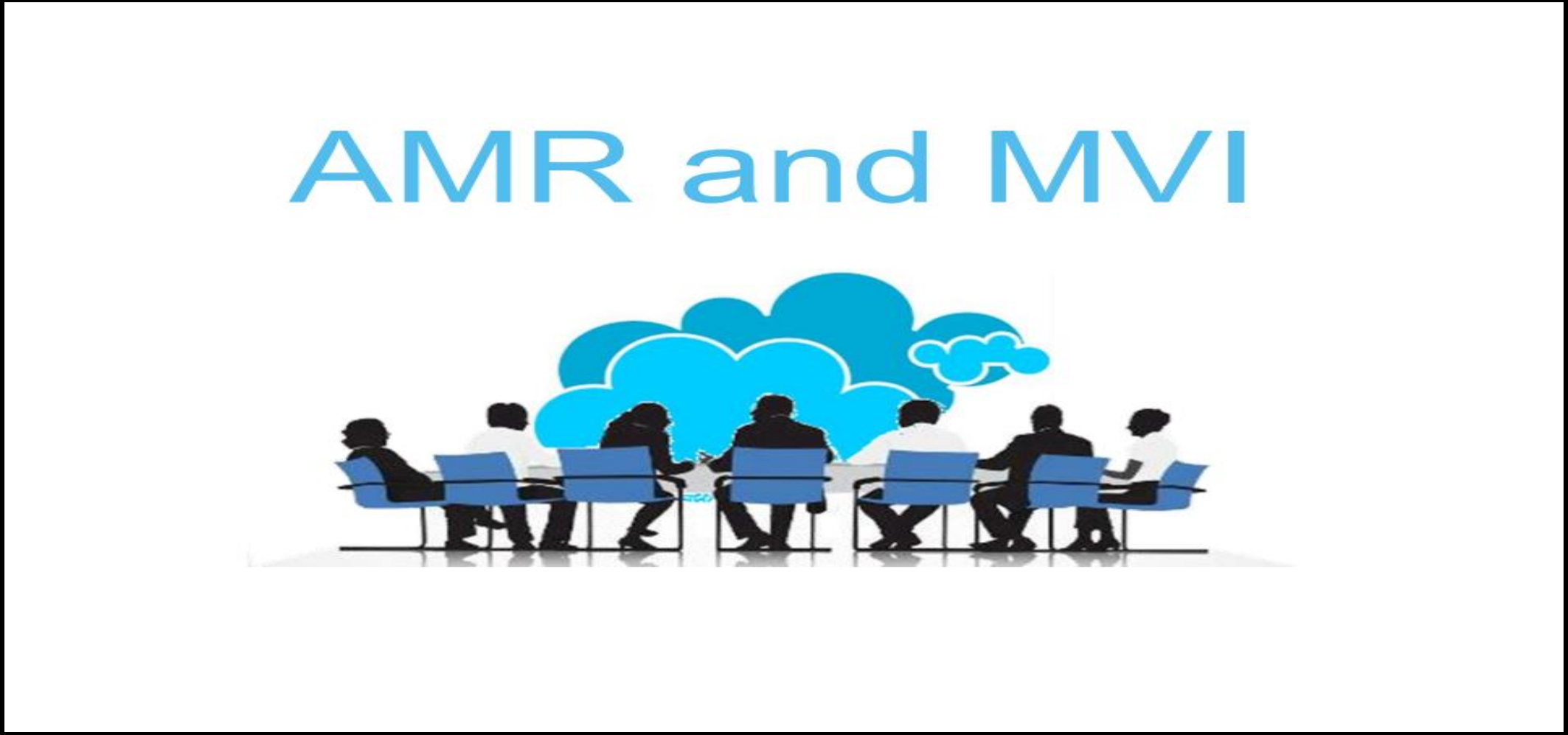
- Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met




Capillaritis

A reappraisal of Microvascular Inflammation as a pathology lesion and its diagnostic specificity: A key focus of the Banff 2022 Kidney Meeting



Microvascular inflammation

In a post meeting survey, agreement was reached on the delineation of the following phenotypes:

(1) "Probable antibody-mediated rejection (AMR),"

which represents donor-specific antibodies (DSA)-positive cases with some histologic features of AMR but below current thresholds for a definitive AMR diagnosis

(2) "Microvascular inflammation,DSA-negative and C4d-negative"

a phenotype of unclear cause requiring further study, which represents cases with microvascular inflammation not explained by DSA.

Before assigning MVI cases as "DSA negative"

The limitations of HLA-DSA testing:

- Incomplete genotyping for all loci including HLA-DP or HLA-DQ
- Technical aspects, and resolution of the assays

should be integrated into clinical decision-making

International consensus in the Banff 2022 Survey on Banff Category 2 definitions of AMR and MVI

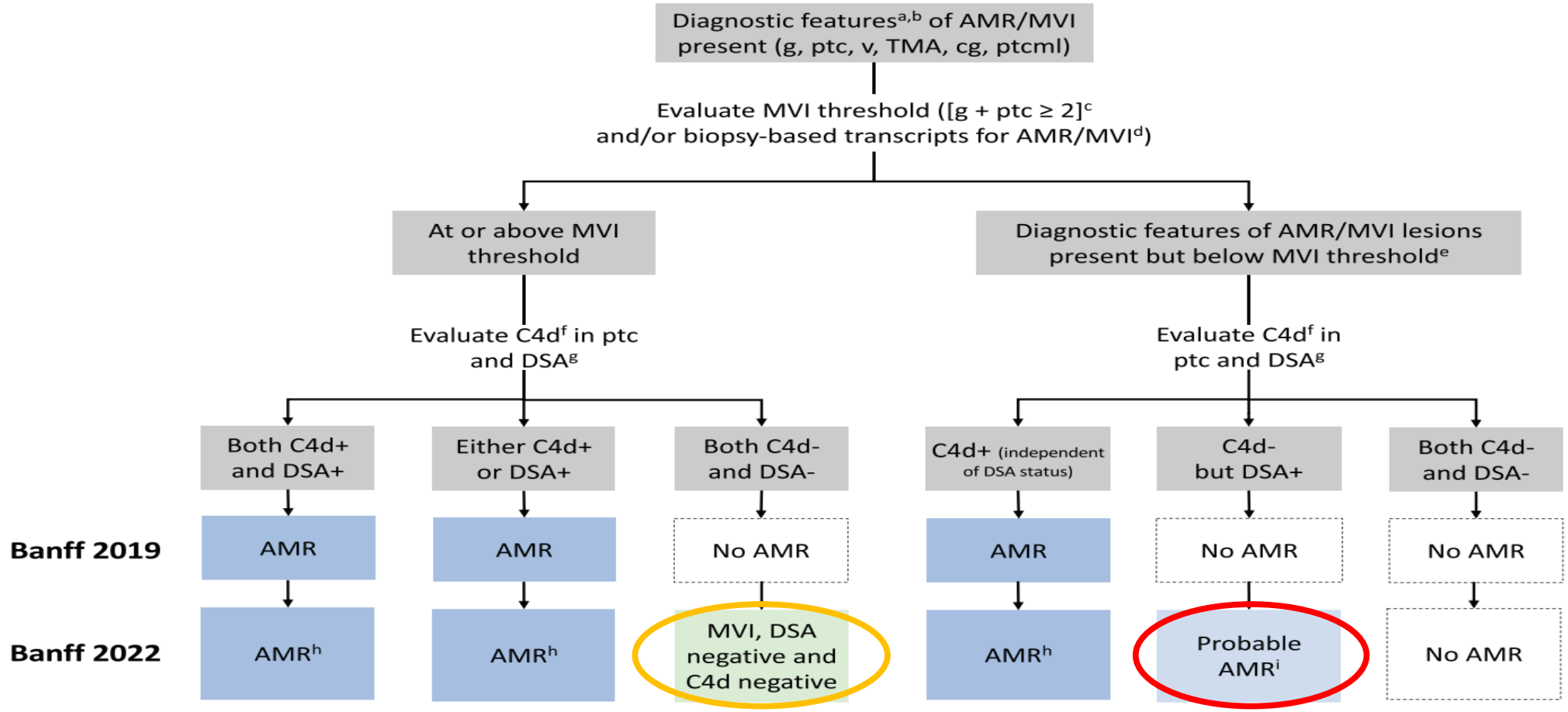


Figure 2. Flowchart of the Banff 2022 Classification for Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI). This can be used as a companion for disease classification but does not modify the detailed Banff Classification for Category 2 AMR/MVI presented in

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"Probable antibody-mediated rejection (AMR),"

- A diagnosis of "Probable AMR" could trigger AMR treatment in certain defined clinical contexts:eg

- In high-risk crossmatch positive transplantations, which are not (yet) associated with severe MVI above the threshold,
- In the case of rapidly declining kidney function in patients with de novo HLA-DSA.

- In other cases, watchful waiting or a repeat biopsy could be considered,

And biopsy-based transcript diagnostics might help, if available.

Further research on this phenotype is necessary

Microvascular inflammation,DSA-negative and C4d-negative

Therapies could be considered for DSA-negative, C4d-negative MVI, in the absence of detectable circulating antibodies,
caution is needed, as the response to those treatments could be low.

Studies that aim to elucidate the causes of the DSA negative C4d-negative MVI phenotype, and targeted therapeutic approaches, are eagerly awaited.

Clinical interpretation of Banff Category 2 - AMR and MVI

Antibody-mediated (AMR)	AMR can be diagnosed in patients with normal or abnormal kidney function. Further differentiation into active AMR, chronic active AMR, and chronic (inactive) AMR, or activity and chronicity indices, can guide therapeutic decision-making.
Probable AMR	In the context of circulating DSA, individual lesions of MVI (also other than g and ptc, i.e., v, TMA, cg, ptcml) below the histological threshold for MVI (g+ptc<2) and in the absence of C4d deposition in peritubular capillaries, probably indicate antibody activity. This can be diagnosed in patients with normal or abnormal kidney function. Depending on the clinical context, antibody-targeted treatment could be considered.
MVI, DSA-negative and C4d-negative	MVI above the histological threshold, without circulating DSA and with negative C4d staining in peritubular capillaries has been observed in patients with normal or abnormal kidney function. This is a purely descriptive category, and the cause remains unclear. Further research is needed to determine the prevalence, the causes and related biological processes and best treatment for this pattern. These cases may represent autoreactive or alloreactive non-HLA antibodies; primary NK cell activation through missing self, viral infection, and other mechanisms of innate immune activation; ischemia reperfusion injury; alloreactive T cell mediated responses, etc.

biopsy-based transcript analysis for diagnosis

- Biopsy-based transcripts were first introduced in the Banff classification in 2013,
- Biopsy-based transcript diagnostics are considered promising and remain an integral part of the Banff Classification

  (limited to diagnosis of AMR)
- further work needs to be done to agree on the exact classifiers, thresholds, and clinical context of use

- Transcript: a sequence of RNA produced by transcription from a DNA template

Clinical comparison between 2 available platforms for biopsy-based transcript diagnostics

Molecular Microscope® Diagnostic System (MMDx)	nCounter B-HOT panel
• MMDx genome-wide microarray panel.	• The consensus B-HOT panel can be applied, but experience is limited.
• Strong and validated relation of MMDx Kidney with the histologic picture of AMR and a weaker relationship with TCMR.[44]	• Initial studies indicate ability to classify AMR and TCMR.[40,45,46]
• Requires a separate core fragment processed at the time of biopsy (but no need for an additional biopsy core).	• Can be performed on FFPE material left over after histologic diagnosis, retrospectively.
• Transcripts in "Molecular AMR" primarily reflect MVI and less C4d or DSA status (no causality).[47-49]	• Transcripts implicated in AMR diagnosis primarily reflect MVI (and potentially DSA status) but not C4d status.[40]
• Technical validity is demonstrated, but statistical measures of variability are not yet reported.[50]	• Many technical questions remain to be answered, eg, regarding normalization and optimal algorithms.[45]
• Clinical validity is demonstrated, and the added value for clinical decision-making suggested. Potential use cases are identified, eg, "subpathological" AMR, DSA-negative MVI, PyVAN, TCMR with isolated v- lesions etc.[51]	• Clinical validity needs to be demonstrated. As with microarrays gene expression changes observed are not always specific for rejection or types of rejection.[52]
• Clinical availability is slowly increasing.	• The strategy for clinical availability requires further development. The ICDOT (International Consortium for Diagnostics and Outcomes in Transplantation; http://icdot.org) platform is proposed as the central repository of B-HOT results for international collaboration on development of validated classifiers.
• The MMDx Kidney platform is licensed for commercial use as a send out test in a CLIA-approved laboratory as a laboratory developed test (LDT), not requiring FDA approval for clinical use in the US. In Europe, the MMDx software is IVD-CE certified as a medical device.	• The technical Nanostring nCounter platform is approved by the FDA (US) and IVD-CE (EU) certified, but the classifiers based on the B-HOT panel are not.

biopsy-based transcript diagnostics

- Despite the major advancements in the analytical validity (ie, technical platform performance) and clinical validity (ie, relation with clinical phenotypes) of biopsy-based transcript diagnostics several central questions relating to clinical utility (value added/cost-benefit) remain unanswered, as emphasized by many members of the Banff community in the Banff 2022 Survey.

Clinical utility is usually taken into consideration by government health agencies, health insurers, or other payers in the decision to cover the cost of testing, and thus the availability of the test to patients.

The Banff Classification in the context of personalized medicine in kidney transplantation

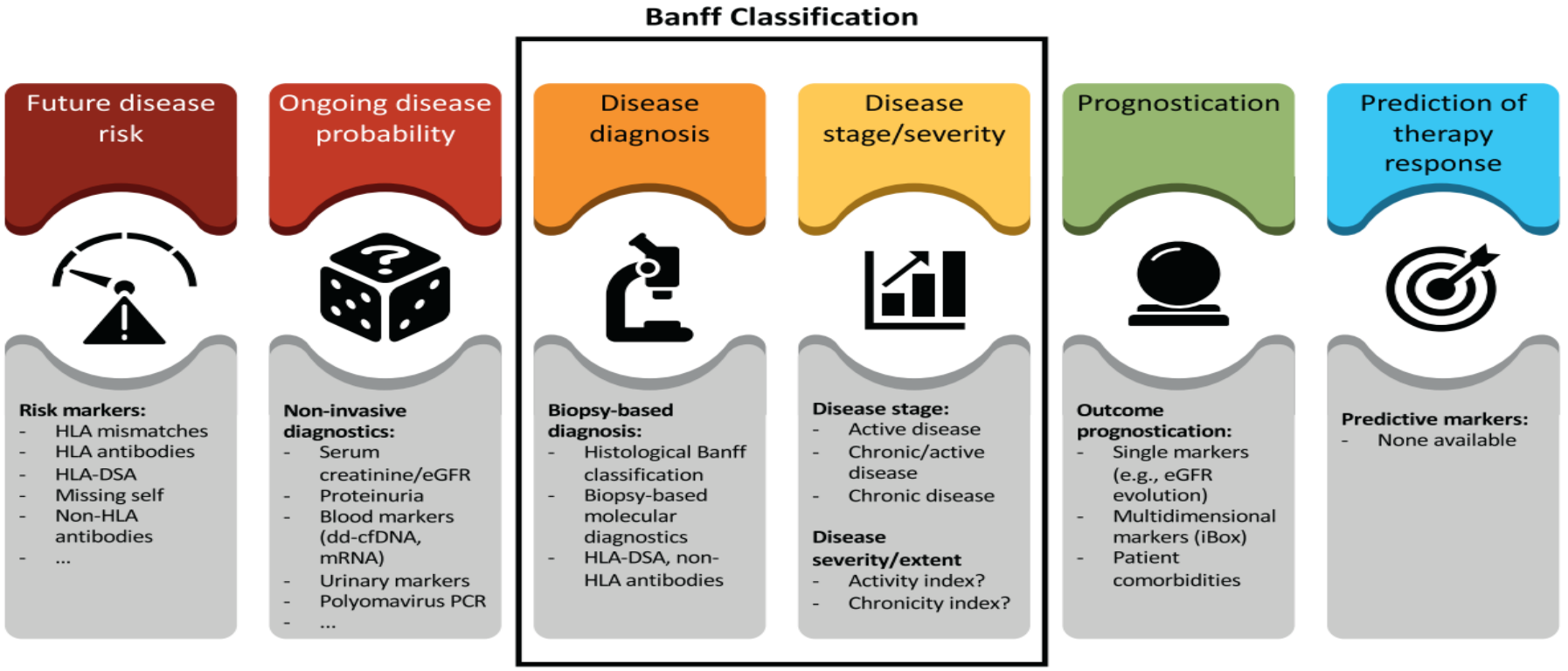

Figure 1. The Banff Classification in the context of personalized medicine in kidney transplantation. The Banff Classification for Kidney Allograft Pathology inscribes itself into a broader framework of personalized medicine and clinical decision support strategies, which can be referred to as "contextualization." This framework includes the following: (1) risk stratification that indicates the potential of developing a disease; (2) noninvasive diagnostic biomarkers that indicate the probability of active disease; (3) biopsy-based diagnostics that confirm the diagnosis (where possible, causal) and specify disease stage/severity (the focus of the Banff Classification); (4) prognostic markers/systems that predict outcome/impact of the disease such as iBox; and (5) predictive markers of therapeutic response guiding specific treatment choices. These very different types of markers/tests should be clearly delineated and not confused, with a very specific context of use for each. In clinical decision-making, all these aspects are considered; an integrated, multidisciplinary approach is essential.

key points

- Banff 2022 update, identifies 2 phenotypes:
  - MVI that are DSA-negative and C4d-negative
  - Probable antibody-mediated rejection (AMR)- (DSA)-positive
- Biopsy-based transcript diagnostics are considered promising and remain an integral part of the Banff Classification

(limited to diagnosis of AMR)

  - further work needs to be done to agree on the exact classifiers, thresholds, and clinical context of use
- The Banff Classification for Kidney Allograft Pathology inscribes itself into a broader framework of personalized medicine and clinical decision support strategies


Thank you for your Attention