Thirty years of the International Banff Classification for Allograft Pathology: the past, present, and future of kidney transplant diagnostics

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2021 marks the 30th anniversary of the original development of the Banff Classification of Kidney Allograft Pathology, when in August 1991 a group of pathologists and transplant clinicians led by Kim Solez and Lorraine Racusen met in Banff, Alberta, Canada, and established the first widely accepted criteria for the diagnosis of kidney transplant rejection and other lesions seen on renal allograft biopsies. Since that time, Banff conferences have been held every 2 years at many sites around the world, resulting in several major revisions to the classification and expansion well beyond pure histopathology of kidney allografts to encompass other solid organ transplants, and with involvement of immunogeneticists, immunologists, other basic scientists, biostatisticians, and data scientists defining a very diverse and integrated Banff community. This approach with multidisciplinary international input, constantly incorporating new evidence from the scientific literature and from studies performed by Banff working groups while still maintaining the importance of a long-standing consensus process, has resulted in the Banff classification gaining overwhelming international acceptance as the main reference used for the scoring of kidney allograft biopsies in research studies, routine practice, and clinical trials. This review focuses on the major milestones in the development of the Banff classification of kidney allograft pathology and the evolution of the Banff process over the past 3 decades, with prospects for future advances and refinements.

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2021 marks the 30th anniversary of the original development of the Banff Classification of Kidney Allograft Pathology, when in August 1991 a group of 12 pathologists and transplant clinicians led by Kim Solez and Lorraine Racusen met in Banff, Alberta, Canada, and established the first widely accepted criteria for the diagnosis of kidney transplant rejection and other lesions seen on renal allograft biopsies, later published in *Kidney International*.[1] Since that time, Banff conferences have been held every 2 years at sites around the world, resulting in several major revisions to the classification and network extensions from a classification based purely on histopathology to the later involvement of physicians and surgeons, immunogeneticists, immunologists, and other basic scientists together with more recent inclusion of biostatisticians and data scientists defining a very diverse and integrated Banff community (Figure 1). This multidisciplinary and international approach has helped the Banff classification gain overwhelming international acceptance as the main reference used for the scoring of kidney allograft biopsies in research studies, routine practice, and clinical trials, making Banff meeting reports among the most cited papers in the field of organ transplantation medicine (Figure 2). Indeed, according to the Web of Science, among the 85,882 items published in the categories of "Transplantation" or "Urology & Nephrology" and dealing with "transplant" and "kidney," 6 of the 15 most cited papers are Banff reports. Establishing the Banff classification system in 1991 marks a major milestone in the field of kidney transplantation. Standardizing renal allograft biopsy scoring was a critical enabler for landmark clinical trials in the field, leading to the regulatory approval of transformative immunosuppressive drugs (e.g., mycophenolic acid and tacrolimus) and thus contributing to improved allograft and patient survival achieved over the past 3 decades. The Banff classification has several unique aspects: (i) It is a self-governed, self-sustained international consensus process independent of established professional and regulatory bodies in the field; (ii) it was, from the beginning, designed as a ordinal scoring system allowing to feed raw data comparable between centers into databases compatible with analytical models including artificial intelligence long before those were invented, but now to be retrospectively validated including long-term outcomes independent of diagnosis

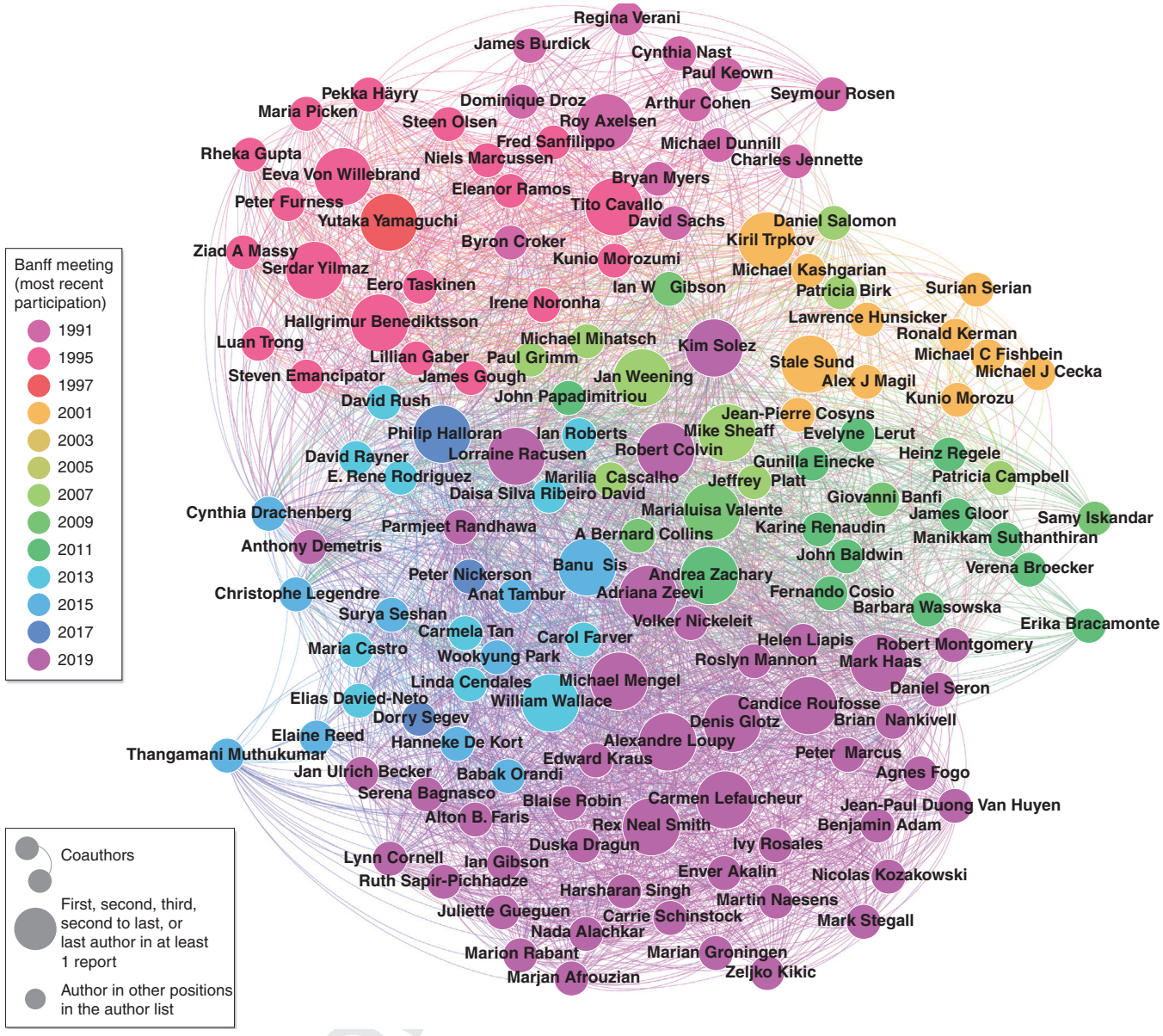

Figure 1 | Banff reports authors landscape 1991 to 2019. This figure is a network graph that depicts the contribution and the interconnections between all the coauthors of Banff meeting reports. Each color represents a different meeting year. Coauthors are connected by lines. Each author is represented by a single bubble. The color of the bubble is that of the last meeting report in which the author was involved (e.g., dark blue if it is the report of the 2017 meeting). The size of the bubble corresponds to the best rank authorship of a report (e.g., a large bubble if the author was first, second, third, next to last, or last author of ≥1 reports). The position of the bubble depends on the coauthorship with the other authors in the landscape (the more the authors have been coauthors, the closer they are).

over various iterations of the classification; and (iii) acknowledged from the beginning to be imperfect, it is therefore designed to be refined and improved as new knowledge emerges, that is, as a learning system.

Because of the coronavirus disease 2019 pandemic and the importance of in-person discussions in the Banff consensus process,[2] the 2021 conference, which was scheduled for Banff Canada in October, was postponed until the fall of 2022. In the interim, as co-organizers of the past 4 Banff conferences and the upcoming conference we have taken this opportunity to summarize 30 years of major milestones as well as to discuss potential future developments in the Banff classification.

BANFF KIDNEY ALLOGRAFT LESION GRADING SYSTEM AND RELATIONSHIP WITH DIAGNOSES

The original Banff classification[1] was based on expert opinion and not on actual data related to graft survival, therapeutic responses, or other outcomes. However, the initial expert consensus was rapidly validated as a relevant clinical end point in major clinical trials, leading to the regulatory approval of transformative drugs such as tacrolimus and

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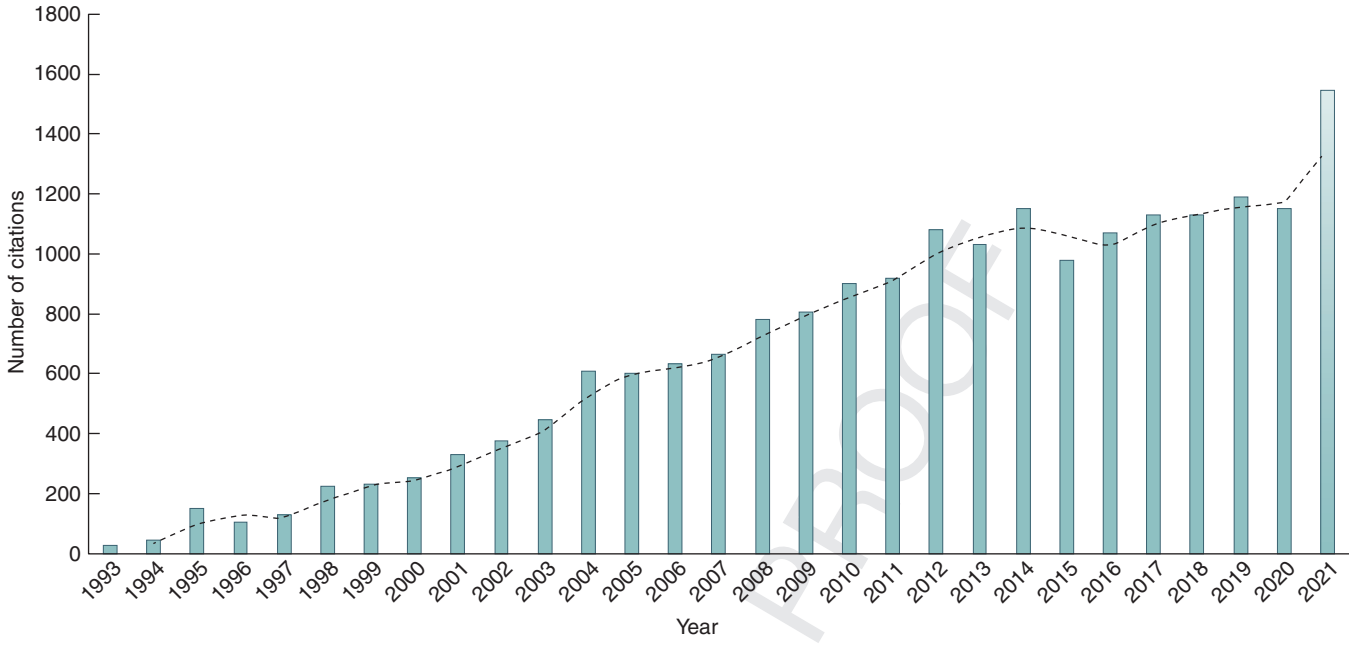

Figure 2| Number of Google Scholar citations related to Banff reports per year (1991–2021). An almost identical trend was observed with PubMed citations.

mycophenolate mofetil. Furthermore, subsequent major modifications to the classification (Table 1; Supplementary Table S1) have been, similarly to, for example, the Oxford classification of IgA nephropathy,[3–5] based on the scientific literature (including specific validation studies) available at the time including the efforts of Banff working groups,[6] which since 2009 have been formed at and report their findings at the biennial conferences. After these presentations, potential revisions to the classification are discussed at designated sessions at each meeting and are adopted, modified, or rejected on the basis of a consensus process involving conference attendees that typically continues for months after the conclusion of the in-person meeting. A high-level summary of the Banff classification evolution including important concepts is provided in Figure 3.

Since the beginning, the Banff classification was designed to render specific diagnoses, the exception being the nonspecific misnomer chronic allograft nephropathy that was discontinued in 2005,[7] before the concept of precision medicine became mainstream. Banff defines 2 pathogenic forms of rejection: T cell–mediated rejection (TCMR) and antibody-mediated rejection (ABMR). These may, in some cases and depending on the timing of the biopsy, occur concurrently (mixed rejection) and may be manifested in a given biopsy in purely active (i.e., clinically acute), chronic active, and purely chronic forms. As noted below, both TCMR and ABMR have strong implications for graft survival and treatment. Derived from observational and mechanistic studies, the Banff classification also defines individual semiquantitative histologic scores for specific lesions that together define acute TCMR (e.g., interstitial inflammation [i], tubulitis [t], and endarteritis [v]), active ABMR (e.g., glomerulitis [g], peritubular capillaritis [ptc], and peritubular capillary [PTC] C4d deposition [C4d]) and chronic changes that may be manifestations of TCMR, ABMR, either, or nonimmunologic lesions such as calcineurin inhibitor nephrotoxicity. As none of these lesions are themselves specific for TCMR or ABMR, these are used for diagnosis when present in certain combinations (e.g., i2 t2 v0 for grade 1A acute TCMR) to increase the diagnostic accuracy and avoid overdiagnosis of rejection. Banff 2019[8] strongly recommends that the biopsy report include the individual lesion scores as well as the diagnosis or diagnoses to provide clinicians with the information to assess the acuity and chronicity, that is, stage and grade, of a given disease process at the time of the biopsy. Furthermore, providing individual lesion scores allows the standardization of biopsy data that can be used for patient evaluation at different centers, in multicenter (including international) clinical studies and trials, and in prediction tools such as the iBox prediction system proposed by Loupy and coworkers, which recently received Food and Drug Administration endorsement as a surrogate end point for clinical trials.[9,10]

BANFF TCMR

The original Banff classification[1] and the first major modification (Banff 1997) of this[11] focused almost entirely on acute TCMR. The 1997 modification was crucial and consisted of unifying the original Banff classification from 1991[1] with that of the National Institutes of Health–sponsored Cooperative Clinical Trials in Transplantation group, led by Bob Colvin.[12] Most notably, this included the distinction of grades 1 and 2 acute TCMR based on the presence of intimal arteritis in the latter. Integrating the 2 classification systems into 1 avoided having multiple approaches toward rejection diagnosis

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Table 1 | Banff classification milestones and supporting scientific evidence associated with classification updates and changes

Q44	**Chronic ABMR:** Several studies highlighted that DSA participate in chronic rejection by demonstrating that DSA are associated with chronic vascular damage and late allograft failure. The recognition that C4d deposition in PTC is associated with histologic chronic lesions, such as transplant glomerulopathy and PTC basement membrane multilayering, led to the elimination of the nonspecific "CAN" and the introduction of chronic ABMR in the classification. The association of transplant glomerulopathy, a key lesion of chronic ABMR, with anti–class II HLA DSA was further confirmed. Several years later it was demonstrated that preformed DSA accelerate post-transplant arteriosclerosis. In 2013, endothelial and glomerular basement membrane lesions detectable early post-transplantation by electron microscopy were highly correlated with later development of transplant glomerulopathy, leading to the acknowledgment of a new cg grade: cg1a.
	v lesion in ABMR: In 2013, a new type of rejection, called "antibody-mediated vascular rejection," was discovered and included in the classification. Moreover, isolated v lesion was recognized as an independent risk factor for allograft failure and was shown to be associated with ABMR and mixed ABMR/TCMR as well as TCMR.
	C4d-negative ABMR: Multiple studies supported the existence of ABMR with negative or minimal C4d deposition. C4d staining previously required for diagnosis was replaced by a category of evidence of antibody interaction with the endothelium in 2013, allowing the acknowledgment of AMR without histologic C4d staining. A new entity was recognized and included into the AMR classification as C4d-negative ABMR. The validity of the threshold for the diagnosis of C4d-negative ABMR in the presence of DSA, (g + ptc) ≥ 2, was confirmed using a molecular approach.
	Subclinical ABMR: Some studies demonstrated that subclinical AMR is common in patients with preexisting DSAs as well as in patients with *de novo* DSAs. Its association with long-term allograft failure was recognized in a population-based study published in 2015.
	Ab properties and phenotypes: During the Banff 2015 meeting, it was acknowledged that the pathogenicity of DSA is heterogenous and that some properties are associated with distinct outcomes. This was based on the demonstration of the ability of DSA to bind complement, and specific IgG subclasses are independent predictors of graft loss.
Q45	**Non-HLA DSA:** The notion of non-HLA DSAs and their impact on rejection emerged in 2005, with the discovery of angiotensin II type 1 receptor activating antibodies. Non-HLA DSAs were included in the classification in 2015 as part of the diagnostic criteria for antibody-mediated rejection. A 2019 study found that AT1R antibodies were associated with decreased graft survival, both in the presence and in the absence of concurrent anti-HLA DSAs.
	Borderline: In 1997, the definition of borderline category was revised. The i score was added to the diagnostic criteria, and its therapeutic management was reconsidered. Using these criteria, it was found that 25%–30% of patients with untreated borderline infiltrates showed progression to acute TCMR (Banff grade 1A or greater) on a follow-up biopsy. In 2005, criteria were changed such that isolated tubulitis (i0t1) was sufficient to define borderline. However, subsequent studies from 2 groups showed that untreated isolated tubulitis was not associated with a significant risk of progressive graft injury, and in 2019 it was agreed that i1t1 is the minimal threshold to define the borderline category.
	ti score: The significance of the lesion score termed "ti" (total inflammation, i.e., inflammation in scarred and nonscarred areas) was demonstrated in 2009. Compared with i and t scores, ti score better reflected molecular phenotypes of the tissue and was also a better predictor of graft survival.
	i-IFTA/chronic active TCMR: The association of interstitial i-IFTA with decreased graft survival was first documented in 2010 and confirmed later by 2 independent groups. Furthermore, these groups demonstrated that i-IFTA is often a sequela of acute TCMR in association with under-immunosuppression. Thus, the classification was revised to include moderate i-IFTA as a component of a diagnostic lesion of chronic active TCMR.
	Transcriptomics: The utility of gene expression analysis was first pointed out in 2003 with the discovery of molecular heterogeneity of rejection using DNA microarray technology. Later, gene sets and molecular classifiers derived from transcriptomic microarray data demonstrated their ability to improve the diagnosis of rejection and the stratification of patients at a high risk of graft failure. A multiorgan transplant gene panel was adopted in 2019: the Banff Human Organ Transplant gene panel.
	Acute → active ABMR: The term "acute" (in acute/active ABMR), which was confusing for the clinicians, was removed from the classification in 2017. This decision was based on a consensus vote and subsequently endorsed in the Banff 2017 meeting report.
	Algorithms/AI prospects: This notion was first introduced in 2019 and was discussed in the form of outcome prediction, digital image recognition, and rejection archetype recognition.

Ab, antibody; ABMR, antibody-mediated rejection; AMR, XXXX; AT1R, angiotensin Q46 type 1 receptor; C4d, peritubular capillary C4d deposition; CAN, chronic allograft nephropathy; cg, transplant glomerulopathy; DSA, donor-specific antibody; g, glomerulitis; HLA, human leukocyte antigen; i, interstitial inflammation; i-IFTA, inflammation within areas of interstitial fibrosis and tubular atrophy; ptc, peritubular capillaritis; PTC, peritubular capillary; TCMR, T cell–mediated rejection; v, endarteritis.

becoming established in the field, which would have presented challenges in the long term, for example, for the enrollment of patients in multicenter trials. Banff 1997 used the original Banff thresholds rather than the Cooperative Clinical Trials in Transplantation thresholds for interstitial inflammation and tubulitis to define grades 1A and 1B acute TCMR with 1 minor revision, namely, including that moderate to severe interstitial inflammation (i2-3) and moderate tubulitis (t2) would be accepted as grade 1B rather than 1A TCMR if at least 2 foci of tubular basement membrane destruction were present.[11] Notably, some additional descriptive elements used in Cooperative Clinical Trials in Transplantation to diagnose acute TCMR (e.g., interstitial edema, activated-appearing lymphocytes, and tubular epithelial injury) were not included in Banff 1997, apparently as these are not sufficiently well-defined although the prognostic impact of these elements was not directly tested. Still, several studies[13,14] have documented progressive increases in corticosteroid resistance and/or graft loss associated with higher grades of rejection according to Banff 1997, with rates of steroid responsiveness and graft survival enhanced in borderline and grade 1A TCMR, intermediate in grades 1B and 2A TCMR, low in grade 2B TCMR, and low to nil in grade 3 TCMR. However, later studies suggested that the poorer outcomes associated with rejection episodes having a vascular component (grades 2A, 2B, and 3) likely reflect a combination of the severity of TCMR plus the presence of a component of ABMR in a fraction of the former cases that was not yet identified at the time of these studies.[15,16]

With the exception of periodic changes in the minimum criteria for borderline inflammation, now accepted to be i1t1,[8,17] before 2017 the criteria for the diagnosis of TCMR remained essentially unchanged from Banff 1997. However,

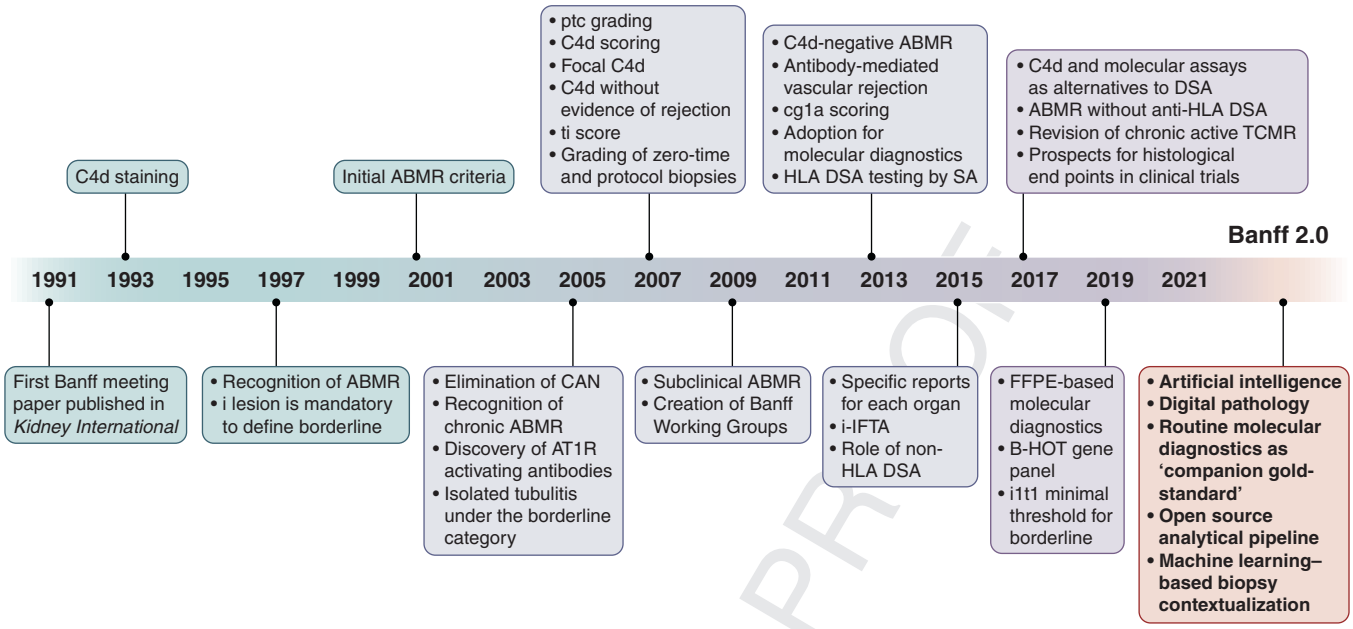

Figure 3 | Evolution of the Banff classification 1991 to 2021: important concepts and changes. ABMR, antibody-mediated rejection; AT1R, angiotensin type 1 receptor; B-HOT, Banff-Human Organ Transplant; CAN, chronic allograft nephropathy; cg, transplant glomerulopathy; DSA, donor-specific antibody; FFPE, formalin-fixed paraffin-embedded; HLA, human leukocyte antigen; i, interstitial inflammation; i-IFTA, inflammation within areas of interstitial fibrosis and tubular atrophy; ptc, peritubular capillaritis; SA, XXXX; t, tubulitis; TCMR, T cell–mediated rejection; ti, total cortical inflammation.

despite this longevity, there have been relatively few studies of its reproducibility. Furthermore, in 3 separate studies, grading of individual lesion scores (i, t, and v) was only moderate at best, with nearly all κ values ranging between 0.34 and 0.50.[18–20] Although in the study of Gough *et al.*,[19] agreement as to the presence or absence of acute TCMR, grade 1A or higher, was good ($\kappa = 0.77$), Veronese *et al.*[20] found a lower κ value (0.57) when borderline lesions were included as acute TCMR. Although interobserver agreement among pathologists in the semiquantitative scoring of interstitial fibrosis and tubular atrophy (IFTA) is generally quite good,[4] agreement in the scoring of inflammation in areas of IFTA, the importance of which is discussed below, remains untested.

An important element of Banff 1997 is that for the diagnosis of borderline and grades 1A and 1B acute TCMR, only nonsclerotic areas of the cortex were considered in determining the interstitial inflammation (i) score and that inflammation within areas of IFTA (i-IFTA) were not considered. However, Mengel *et al.*[21] found that total cortical inflammation (ti score) was more predictive of graft outcomes than the i score and the DeKAF study[22] found that the extent of i-IFTA was an independent predictor of graft loss. Thus, at the 2015 Banff meeting criteria for grading i-IFTA on a semiquantitative scale (0–3, much like i and with similar thresholds) were adopted,[23] although i-IFTA was still not considered in diagnosing TCMR. Subsequent to Banff 2015, several independent groups[24–27] validated these results and also added the key result that i-IFTA is associated with previous episodes of acute TCMR,[24,25] strongly suggesting that i-IFTA is often a sequela of acute TCMR and may also be a manifestation of underimmunosuppression,[25,28] as well as a more negative impact of i-IFTA on graft survival when concurrent tubulitis is observed.[24]

Based on these findings, in Banff 2017[29] a category of chronic active TCMR was added to the classification. Recognizing that i-IFTA is clearly not specific for TCMR and can result from multiple etiologies including ABMR, polyomavirus nephropathy, and nonimmunologic lesions, which need to be ruled out before diagnosing chronic active TCMR,[26,30] the diagnostic criteria for chronic active TCMR grades 1A and 1B were designed to be relatively stringent, including not only at least moderate i-IFTA but also at least moderate total inflammation and tubulitis.[29] Banff 2019[8] also allows for the concurrent diagnosis of acute and chronic active TCMR when criteria for both are met; this is particularly pertinent when there is chronic active TCMR grade 1A or 1B plus intimal arteritis. Recent preliminary data[31] indicate that treatment of chronic active TCMR can in some cases improve allograft function and that responsive cases were not limited to those also meeting criteria for acute TCMR, further supporting the most recent revision of the Banff classification. However, the majority of cases in this study, including most grade 1B cases, were resistant to treatments used for acute TCMR (mainly corticosteroids). Molecular analysis of gene expression in the biopsy tissue was promising in differentiating steroid-sensitive versus steroid-resistant chronic active TCMR and a multicenter validation study of this is in its early stages.

BANFF BORDERLINE CATEGORY

The Banff borderline category has been a problematic aspect of the Banff classification virtually since its inception, and

indeed there have been suggestions that it should be eliminated.[32] As noted above, the diagnostic criteria for this lesion have been changed twice. The first such change, originally suggested in Banff 2005[7] and confirmed in Banff 2007,[33] changed the minimum threshold for borderline from i1t1 to include tubulitis (t ≥ 1) with "minor" interstitial inflammation (i0 or i1), although no specific rationale was given for this change and a 2016 Renal Pathology Society survey[34] showed that despite this change, 93 of 139 responding pathologists (67%) continued to use the i1t1 threshold to define borderline. Banff 2019[8] officially restored the original threshold of i1t1 on the basis of studies from 2 groups demonstrating that untreated isolated tubulitis was not associated with a significant risk of progressive graft injury.[35,36] A pressing and long-standing problem remains whether clinicians should in fact treat patients with borderline lesions for acute TCMR. Data indicate that at least some borderline lesions do in fact represent an alloimmune response that may reflect under-immunosuppression[28]; may be associated with elevated serum levels of donor-derived cell-free DNA, a marker of graft inflammation and injury[37]; and, in the context of indication biopsies, show a clinical response to steroid therapy.[13,38] Although borderline lesions (with threshold i1t1) have been shown to be associated with an increased risk of subsequent TCMR (Banff grade 1A or greater),[39] other evidence suggests that many borderline lesions, if untreated, do not progress to acute TCMR grade 1A or greater[40] and may be manifestations of the wound healing process related to nonimmune injuries.[32] Again, the potential value of molecular approach in identifying specific diagnoses for the borderline category and potentially eliminating this nonspecific category will be discussed below.

BANFF ABMR

Diagnostic criteria for acute/active ABMR were first added to the Banff classification after the 2001 conference[41] with a requirement for histologic criteria (microvascular inflammation [MVI]), immunohistologic criteria (C4d staining in PTCs), and donor-specific antibody (DSA) to all be present for diagnosis. Criteria for chronic active ABMR, with histologic criteria for transplant glomerulopathy (cg), PTC basement membrane multilayering (ptcml), and transplant arteriopathy (cv), were added later.[33,42] From Banff 2001 to Banff 2011, only diffuse C4d staining, involving >50% of PTCs, was accepted as meeting the immunohistologic criterion for ABMR, although this was changed in Banff 2013 to accept focal (10%–50%) PTC staining that had been shown to be associated with DSA and reduced allograft survival.[43] Based on a study comparing C4d staining by indirect immunofluorescence on frozen sections of fresh tissue and immunoperoxidase on sections of formalin-fixed paraffin-embedded (FFPE) tissue,[44] Banff 2013 also accepted C4d-positive minimal staining (>0 but <10% of PTCs) by immunoperoxidase on FFPE tissue but not by immunofluorescence on fresh frozen tissue. In addition, in Banff 2013 the minimum criteria for glomerulitis (g1) and chronic glomerulopathy by light microscopy (cg1) were updated on the basis of working group data showing improved (albeit still only moderate) interobserver agreement with these criteria.[42] The potential importance of electron microscopy was also given new emphasis, with the introduction of specific criteria for ptcml to improve the specificity of this lesion for chronic ABMR[45] and the incorporation of a new lesion of chronic glomerulopathy by electron microscopy only (cg1a) on the basis of previous studies[46,47] showing that electron microscopy findings of early glomerular basement membrane duplication plus glomerular endothelial swelling and/or subendothelial electron lucent widening were highly associated with the subsequent development of overt transplant glomerulopathy, particularly in patients with DSA who were not specifically treated for acute ABMR.

The first major modifications to the ABMR classification were also made in Banff 2013.[42] These updates were a direct response molecular study of Sis *et al.*[48] and a protocol biopsy study of Loupy *et al.*,[49] which provided the first strong evidence that DSA could produce chronic graft injury including transplant glomerulopathy leading to graft loss in the absence of complement (C4d) deposition in the capillary endothelium. The absolute requirement (criterion 2) for PTC C4d staining for the diagnosis of active or chronic active ABMR[33,41] was thus changed to a requirement for evidence of the recent interaction of antibody with the microvascular endothelium, the latter including C4d but alternatively at least moderate MVI (g + ptc ≥ 2) or increased expression of validated gene transcripts in the biopsy tissue indicative of endothelial injury, representing the initial inclusion of molecular diagnostics in the classification.[42] An important and sometimes overlooked caveat in the diagnosis of ABMR is that peritubular capillaritis (a ptc score of 1 in C4d-positive cases and a ptc score of ≥2 in C4d-negative cases) without glomerulitis is acceptable only as a diagnostic criterion if there is no accompanying TCMR (including borderline) or interstitial inflammation secondary to infection; in such cases, at least mild glomerulitis (g1) must be present for diagnosis. As with earlier iterations of the Banff ABMR criteria, in Banff 2013, biopsies meeting 2 or 3 diagnostic criteria (e.g., not fully meeting criterion 2 as noted above or lacking identifiable anti–human leukocyte antigen [HLA] or other antibodies directed against the graft) were termed "suspicious for ABMR."[42] The histopathologic scope of ABMR was further expanded by studies strongly suggesting that active arterial lesions other than fibrinoid necrosis, namely, intimal arteritis (endarteritis), could be a manifestation of active ABMR rather than, or more often in addition to, acute TCMR.[15,42] Notably, the 2013 modification of the ABMR criteria led to an approximate doubling of the diagnosis rate for ABMR, which is not a surprising figure because in most series 25% to 50% of cases of ABMR are C4d negative, this fraction being dependent on a number of factors including method of C4d detection (immunofluorescence vs. immunoperoxidase), whether focal C4d staining was counted as positive, and predominance of biopsies performed early versus later post-

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transplantation.[50–53] Notably, however, there was also a significantly stronger association of an ABMR diagnosis with a composite end point of graft loss or doubling of serum creatinine.[52] The latter finding is consistent with previous studies showing that in highly sensitized cohorts of kidney recipients with preexisting DSA, MVI was associated with worst allograft outcome independently of C4d positivity,[54] although C4d-negative ABMR may represent a milder form of ABMR, perhaps related to noncomplement fixing antibodies.[48,50] Furthermore, there is now strong evidence that individual histologic lesions of active ABMR (g and ptc) are precursors of chronic ABMR lesions (cg and ptcml),[55–57] similar to the case with TCMR lesions (i, t, and i-IFTA) as discussed above.[24,25]

ANTIBODY DETECTION AND CHARACTERIZATION IN THE BANFF CLASSIFICATION: HLA SYSTEM AND BEYOND

The presence of donor-specific anti-HLA antibodies is a key component of the diagnosis of ABMR in kidney and other solid organ transplants. Hence, although Banff 2013 clearly represented an improvement in both the overall accuracy of ABMR diagnosis and the prognostic value of such a diagnosis, there were still significant numbers of cases that could not be definitely classified according to Banff 2013, with a substantial fraction of these represented by those with MVI in the absence of detectable anti-HLA DSA. It is noteworthy that Banff 2013 and subsequent iterations of the ABMR classification do not limit the serologic criterion (criterion 3) for ABMR diagnosis to antibodies against HLA, but rather specify that the antibodies may be directed against "HLA or other antigens."[42] This is important as subsequent studies demonstrated that antibodies against angiotensin type 1 receptor and other non-HLA antibodies can produce histologic changes of ABMR in the absence of anti-HLA DSA.[58–60] However, as the full range of non-HLA antibodies capable of injuring the allograft and their related pathology is not currently known,[58] many centers currently do not test for non-HLA antibodies, and biopsies meeting morphologic criteria for both active and chronic active ABMR in the absence of anti-HLA DSA often fall into the "suspicious for AMR" category, leaving the clinician unsure as to whether to treat ABMR.

In this context, additional updates to the ABMR classification were made at the 2017 conference[29] in an attempt to limit the number of such equivocal situations. As linear C4d staining in PTCs is ≥90% specific for humoral immunity,[61–63] such staining is now accepted as a surrogate marker for DSA in criterion 3 of the classification.[8,42] In addition, recommendations were made for molecular testing in biopsy to provide evidence for antibody interaction with the microvascular endothelium.[64,65] The fact that molecular diagnostics are presently used at only a small number of centers is a limitation of Banff 2017/2019, but hopefully the use of such testing will become more accessible as discussed below.

In contrast, the modifications to the classification discussed above, while aimed at improving the diagnostic and prognostic value of the classification and helping to guide therapeutic approaches to patients undergoing kidney allograft biopsies, have also come with a price: increased complexity.[66]

To address this issue, the Banff consortium is engaged in several efforts aimed at helping resolve many of the complexities of the Banff classification. A major objective of the Banff 2019 meeting report[8] was the clarification of definitions for individual histologic lesion scores and all diagnostic categories, including active and chronic active ABMR, TCMR (including acute, chronic active, and borderline), and polyomavirus nephropathy as defined by another Banff working group.[67]

Finally, at the Banff 2019 conference, initial discussions were held regarding simplifying the classification itself. A Banff survey on clinical practices in patients diagnosed with ABMR found the classification was felt to be complex and vulnerable to misinterpretation, leading to heterogeneity in whether patients, particularly those with chronic active ABMR, received treatment specifically directed at ABMR.[66] One proposed approach was to eliminate separate categories for active/acute, chronic active, and chronic rejection, replacing these with single categories of ABMR and TCMR plus measures of activity and chronicity, determined from individual lesion scores, much as has been done with the International Society of Pathology/Renal Pathology Society classification of lupus nephritis.[68] Preliminary studies presented at that meeting (M. Haas, unpublished results) showed that in 80 previously reported cases of active or chronic active ABMR, with or without concurrent TCMR and all with anti-HLA DSA and all treated for ABMR,[53] a chronicity score of ≥4, determined from the sum (ci + ct + cv + cg[x2]), was an independent predictor of decreased graft survival. By contrast, an activity index (g + ptc + v + C4d) was not predictive of graft survival, although the sum (g + ptc) was predictive according to univariate analysis only; these findings are consistent with studies showing that the most predictive molecular features for graft loss in ABMR were those associated with active and chronic tissue injury rather than those associated with MVI.[69] This is potentially important not only in simplifying the classification of ABMR but also in aiding clinicians in making treatment decisions, especially in patients diagnosed with chronic active ABMR and with new and promising treatments for this now available. It suggests that low-level transplant glomerulopathy (cg1), which for even experienced pathologists can be a problematic diagnosis (M. Mengel, M. Haas, R. Colvin, unpublished observations), should not be a contraindication to treatment of ABMR, particularly if there is little or no IFTA.

MIXED REJECTION (ABMR + TCMR)

Banff does not a have specific diagnostic category of mixed rejection, but as noted above, the ABMR criteria contain an important provision to limit overdiagnosis of this, namely, that in the presence of TCMR or borderline inflammation, peritubular capillaritis alone, even if severe, is not sufficient to satisfy the morphologic criteria for ABMR diagnosis and

glomerulitis must be present.[42] Even so, mixed rejection remains a frequently observed lesion that has important implications regarding prognosis for and therapeutic approach to the patient. In 147 patients initially diagnosed with active or chronic active ABMR at Cedars-Sinai Medical Center over a 9-year interval (2010–2018), 47 (32%) also had TCMR (Banff 1A or greater), and it was previously shown that concurrent TCMR is a significant risk factor for graft loss in patients with ABMR by univariate analysis, with borderline significance by multivariable analysis.[53] Although it is commonly felt that mixed rejection is mainly seen in biopsies performed late post-transplantation, in these 147 patients nearly half of such cases (45%) were seen <2 years post-transplantation, and similar fractions (47% vs. 53%) were seen with active and chronic active ABMR, respectively.

SUBCLINICAL REJECTION

The Banff criteria for TCMR and ABMR do not differentiate between biopsies performed for clinical indication and protocol biopsies, and many of the studies validating the clinical applicability of these criteria and leading to modifications in the criteria contained combined findings from indication and protocol biopsies. Still, it is worth considering the applicability of the classification in directing potential therapeutic interventions in response to subclinical TCMR or ABMR, that is, diagnosed on a protocol biopsy of a stably functioning graft. Rush and Gibson[70] recently reviewed the topic of subclinical TCMR. Their basic conclusion, based on their multiple investigations in this area, is that subclinical TCMR (and perhaps even subclinical inflammation not meeting Banff criteria for TCMR) is often the result of inadequate baseline immunosuppression and can lead to the development of IFTA and i-IFTA, *de novo* DSA, declining graft function, and even graft loss.[70] Studies from the Sydney, Australia group based on large numbers of biopsy samples that were primarily, although not exclusively, protocol biopsies yielded similar conclusions, with a progressive increase in the risk of subsequent graft scarring and loss as the degree of subclinical inflammation increased from less than borderline to borderline to grade 1A acute TCMR.[17] However, although Hoffman *et al.*[71] found that subclinical TCMR was associated with chronicity scores at 3 and 12 months post-transplantation that were intermediate between those seen in nonrejecting grafts and those with clinical TCMR, unlike the latter, subclinical TCMR during the first year post-transplantation was not a significant predictor of a subsequent rise in serum creatinine.

Protocol biopsies have been crucial in establishing the links between lesions of acute (g and ptc) and chronic (cg and ptcml)[49,55–57] histologic lesions of ABMR, and the seminal study of Loupy *et al.*[49] clearly established in DSA-positive patients that subclinical ABMR, both C4d positive and C4d negative, is associated with a decline in allograft function. Still, recent studies suggest that MVI (g + ptc ≥ 2) diagnosed on early protocol biopsies in the absence of anti-HLA DSA, even with positive C4d and thus meeting Banff 2017/2019 criteria for active ABMR, may represent a relatively benign lesion.[72]

MOLECULAR DIAGNOSTICS IMPLEMENTATION IN THE BANFF CLASSIFICATION

At the 2001 Banff meeting, for the first time, results of molecular studies applied to transplant biopsies were presented. Since then, molecular topics have been part of the scientific program of every Banff meeting, allowing the group to monitor, review, and discuss the progress of research done in molecular transplant diagnostics. The ultimate aim has always been to improve diagnostic precision by integrating molecular diagnostics into the Banff classification, similar to the integration of other ancillary diagnostic tests such as C4d staining and DSA testing.

In 2013 the Banff consortium for the first time officially added molecular diagnostics to the Banff classification (Figure 3).[42] The initial focus was on endothelial cell–associated transcripts, which when overexpressed in the biopsy tissue were found to be associated with an increased risk of graft loss, even in the absence of C4d staining.[48] Endothelial gene overexpression was thus included as a diagnostic feature equivalent to C4d for the diagnosis of ABMR. This was a forward-looking proposal because there was no consensus about which endothelial genes should be quantified and no independent multi-institutional validation for any diagnostic classifier or gene set. Starting with Banff 2017, the focus shifted away from just endothelial genes toward molecular classifiers based on multiple transcripts differentially expressed in biopsies with and without morphologic features of ABMR that were demonstrated to be predictive of DSA-mediated tissue injury and graft loss.[64,65] In addition to gene transcripts expressed in endothelial cells, the molecular classifier developed by Halloran and coworkers includes transcripts expressed in other cells known to be involved in the pathogenesis of antibody-mediated graft injury, including natural killer cells and macrophages.[64]

The main impetus in 2013 was to adopt a molecular diagnostic option into the classification, despite these limitations, and to set the future direction for the Banff classification: promoting a collaborative and multi-institutional, open source efforts to advance the field by validating, but also standardizing and making molecular transplant diagnostics accessible to the broad transplant community. The latter has always been a foundational core value of the Banff consortium.[2,73] Indeed, the value of this early introduction of molecular diagnostics soon came to fruition, as it was a molecular study of transcript sets previously found to be increased in biopsies with ABMR[64,74] that provided key evidence supporting the (g + ptc) ≥ 2 threshold for the diagnosis of C4d-negative ABMR in the presence of DSA.[75] Still, owing in large part to cost issues as well as the need for additional tissue for molecular analysis using the initially applied molecular methodologies (the latter not only adding inconvenience for the patient but also a potential source of discrepancy with histologic findings because of sampling of

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different areas), use of molecular diagnostics in the analysis of renal transplant biopsies remains limited to a relatively small number of centers, mainly in North America and western Europe, although the development of different technologies for the analysis of these biopsies may be a partial solution as discussed below. A major issue for clinicians as well as pathologists is when to use molecular diagnostics, as its routine application is not feasible at present. This was reviewed in Table 1 of a commentary by Haas in *Kidney International*,[76] which suggests that submission of tissue for molecular testing is best considered when biopsy results are equivocal for making treatment decisions, such as with biopsies showing changes suspicious but not diagnostic for rejection, especially ABMR, and with biopsies of ABO-compatible grafts showing PTC C4d staining in the presence of DSA but without histologic changes of rejection, which in some but not all cases may represent a *forme fruste* of ABMR.[77,78]

The 2015 Banff meeting[20] focused on a gap analysis between current clinical practice and the clinical implementation of standardized and validated molecular diagnostics in transplantation, with the recommendation to generate molecular consensus gene sets (or classifiers) from the overlap between published and reproduced gene lists that associate with the main diagnostic phenotypes (TCMR, ABMR, infection, and acute kidney injury). To this end, collaborative multicenter studies were proposed to close identified knowledge gaps before Banff can fully adopt specific molecular diagnostics as part of the classification. Accordingly, consensus had to be generated on gene sets, which then can be investigated in a multicenter setting, with the results then being reviewed at future Banff meetings as part of the ongoing iterative consensus process for molecular diagnostics.

At the 2017 Banff meeting, a first draft of a consensus gene list was reviewed and potential specific indications for ancillary molecular testing were identified.[29] Importantly, application of a new technology that is able to provide robust and comprehensive molecular testing on FFPE biopsies was presented for the first time, with the compelling advantage that performing transcriptional analysis and routine histologic assessment on the same sample allows for direct histo-molecular integration of the findings.[79,80]

Q29 On biopsy material, most of the published research studies on molecular testing used microarray technology performed on an extra biopsy core stored in RNAlater Stabilization So-
Q30 lution. A commercial test (Molecular Microscope MMDx, One Lambda Inc.) derived from these studies has recently been launched into the market. Multicenter studies have been performed using the MMDx assay as centralized referral laboratory testing.[81–84] These nonrandomized studies revealed strong associations with the histologic Banff lesions and diagnosis, but also identified discrepancies between the current Banff classification applied to histology and reads on
Q31 corresponding but separate biopsy cores.[85]

More recently, the initial results derived from FFPE biopsy analysis have emerged, in particular the NanoString nCounter
Q32 analysis system, with several publications now reporting molecular analysis in FFPE transplant specimens studying the expression of gene sets comprising the top genes overlapping between previously published microarray studies while finding similar associations between molecular and histologic phenotypes.[31,78–80,86] Beyond the advantage of being performed on the same sample used for light microscopy, FFPE-based technologies offer the opportunity for large retrospective and longitudinal analyses of archived samples in the setting of decentralized multicenter studies, that is, allow for retrospective randomization with survival end points available.[87] The nCounter system is approved for clinical diagnostics and paired with user-friendly analytical software, thus representing a simple, relatively fast (24-hour turnaround time), automated platform that is well poised to be integrated into the routine diagnostic workflows in existing pathology laboratories while making results reproducible and comparable between laboratories.

In addition to tissue-based approaches, several body fluid assays for diagnosing or ruling out rejection from blood samples have been launched commercially (e.g., kSORT [Immucor DX], AlloSure [CareDx], Plasma Prospera [Natera], and TruGraf [Viracor-Eurofins]).[88] Up to now, the
Q33 sensitivity and specificity of these tests are insufficient to allow using these noninvasive molecular diagnostics as a replacement of the invasive biopsy procedures, as none of the proposed markers seem sufficiently specific for the detailed phenotypic heterogeneity of transplant pathology. However, noninvasive tests allow for better risk stratification and guide decisions when to perform a biopsy in a given patient with the aim to diagnose, grade, and stage diseases present.[89–91]

THE NEXT 30 YEARS OF THE BANFF CLASSIFICATION: 2022 AND BEYOND

Changing the current design and operating pipeline of molecular diagnostics

Consensus gene set adoption. In 2019 as a joint effort to promote adoption of tissue-based molecular testing in routine diagnostics, the Banff working group for molecular diagnostics established a consensus gene panel based on a data-driven approach—the Banff-Human Organ Transplant (B-HOT) gene panel.[92] The B-HOT panel includes 770 genes
Q34 (including 12 internal reference genes for quality control and normalization) covering the most pertinent genes and gene sets (including endothelial cell–associated transcripts and other pertinent pathogenesis-based transcripts as first described by Halloran and coworkers) from the core molecular pathways and processes related to host responses to rejection of transplanted tissue, tolerance, drug-induced toxicity, and transplantation-associated viral infections (BK polyomavirus, cytomegalovirus, and Epstein-Barr virus). The panel was designed to cover these aspects across the different organ types for transplantation, and the probes were chosen for sequential homology with nonhuman primates to facilitate preclinical research applications. Although the B-HOT panel is commercialized through NanoString Technologies Inc. (Seattle, WA) for use on the nCounter system, the gene
Q35 list is not proprietary and can be studied on any other

analytical platform. The B-HOT panel represents the foundational molecular consensus reflecting the core molecular "lesions" in an allograft, similar to the histologic consensus of the core histopathologic lesions established 30 years ago in Banff, Canada. Based on this consensus, any potential clinically useful molecular diagnostic test derived from the B-HOT panel can be analytically and clinically validated in the multicenter setting while generated raw and metadata are comparable between centers, analogous to the Banff histology lesion scores and diagnoses.

Building an open source repository and analytical platform for decentralized molecular diagnostics. To facilitate multicenter validation of the B-HOT panel and its derivatives, members of the Banff working group for molecular diagnostics are aligning their efforts in studying a broad spectrum of archived and well-annotated transplant biopsies. All participating centers will input clinical, pathologic, and molecular data into a shared integrated data platform for joint analysis in the multicenter setting (https://www.icdot.org). This crowd-sourced data-sharing consortium will allow the standardization of molecular testing across laboratories and multicenter analytical validation and clinical validation of any diagnostic assays, including the definition of diagnostic and clinically relevant thresholds for molecular measurements.

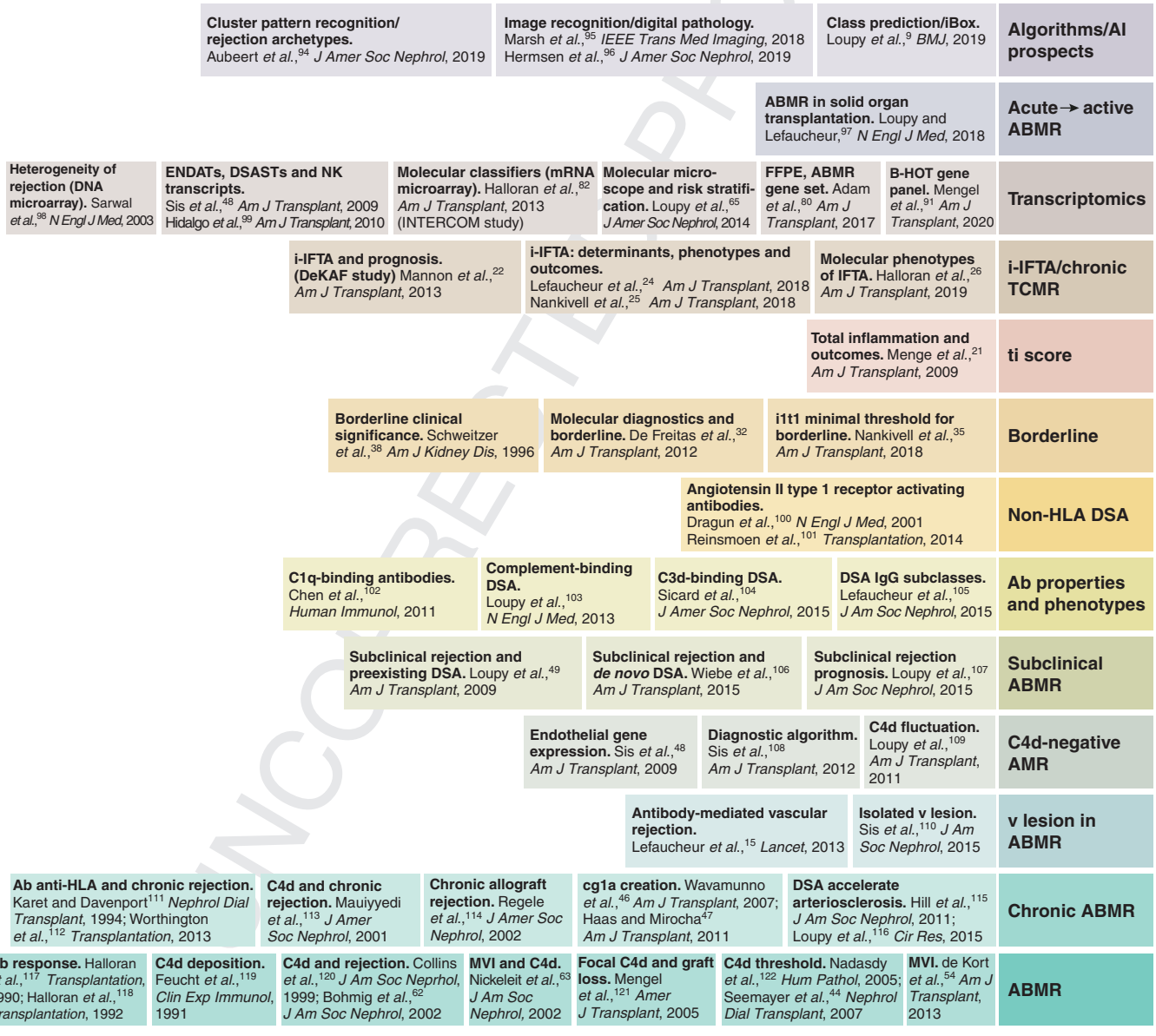

Figure 4 | Banff classification milestones and supporting scientific evidence associated with classification updates and changes. Reference numbers correspond to those in the list of references. Ab, antibody; ABMR, antibody-mediated rejection; AI, artifical intelligence; AMR, XXXX; B-HOT, Banff-Human Organ Transplant; cg, transplant glomerulopathy; DeKAF, XXXX; DSA, donor-specific antibody; DSAST, XXXX; ENDAT, endothelial cell–associated transcript; FFPE, formalin-fixed paraffin-embedded; HLA, human leukocyte antigen; i, interstitial inflammation; IFTA, interstitial fibrosis and tubular atrophy; i-IFTA, inflammation within areas of interstitial fibrosis and tubular atrophy; MVI, microvascular inflammation; NK, natural killer; t, tubulitis; TCMR, T cell–mediated rejection; ti, total cortical inflammation; v, endarteritis. Q43

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Such international, open source, multicenter Banff data platform can serve as a reference point for generating a molecular diagnostic "gold standard" in transplantation, similar to the Banff histologic lesions and diagnoses first agreed upon in 1991.[1] With new knowledge and technologies emerging, the Banff rules for histology underwent constant refinement over the past 30 years. Similarly, any molecular "consensus" will need to undergo ongoing refinement toward the ultimate goal of diagnostic precision in transplantation.

Artificial intelligence Banff: integrative multimodality and machine learning–driven diagnostics

During the 2019 Banff meeting, there was an emphasis on projects with usage of artificial intelligence, machine learning, and deep learning. There has been focus on classification, clustering, as well as image analysis from digital pathology. Reading digital biopsies accurately by a machine is not a simple task and has always been a challenge even with most advanced image analyzing algorithms such as convolutional neural network. Although the present results are preliminary, it is promising that this approach is being more researched[92,93] and getting more accurate with time and could ultimately improve the Banff classification.

Another topic of interest highlighted was the need for data-driven unsupervised statistical approaches such as archetypes to define a patient of interest contextualized in a reference standard of patients sharing similar patterns.[94]

Such methodology describes each biopsy as a composite of the underlying archetypes. Although the aim of archetype analysis is not to assign a specific diagnosis, it allows precise probabilistic assessment while retaining the uniqueness of each patient. By applying this approach to a large comprehensively phenotyped multicenter cohort of kidney transplant recipients, distinct archetypes with distinct clinical, histologic, and immunologic features as well as different outcomes can be identified, suggesting that machine learning–based characterization may improve risk stratification for individual patients undergoing kidney transplant and those included in clinical trials. Finally, because the Banff rules are becoming complex to follow with numerous possible scenarios, there were emerging demands for automated Banff coded algorithms. This task will be challenging because it requires integration between skilled pathologists to decode the Banff rules and computer and data scientists to create an algorithm to deal with at times counterintuitive Banff rules.

The future for the Banff classification is bright. Just as the first 30 years of Banff have provided many important milestones, summarized in Figure 4,[9,15,21,22,25,26,32,35,38,44,46–49,54,62,63,65,80,82,91,94–122] the next 30 years offer ample opportunity to increase our precision and accuracy in diagnosing, staging, grading, and thus stratifying our patients for the optimal treatment(s) and thus further improved allograft survival. The iterative learning Banff process is designed to constantly improve and embrace new knowledge and technologies as they emerge. The authors, on behalf of the transplant community, are grateful to the visionary thinking and 30 years of leadership by Drs. Lorraine Racusen, Kim Solez, and Robert Colvin.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1A. Supporting literature cited by Banff reports: antibody-mediated rejection (ABMR).

Table S1B. Supporting literature cited by Banff reports: antibody properties, transcriptomics, and artificial intelligence–based systems.
Table S1C. Supporting literature cited by Banff reports: Borderline and T cell–mediated rejection (TCMR).
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