Meeting Report: The First Global Congress on Epidermolysis Bullosa, EB2020 London: Toward Treatment and Cure

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Introduction to EB2020: Challenges and unmet needs

Epidermolysis bullosa (EB), the prototype of skin fragility disorders, manifests with blistering and erosions, associated with a number of extracutaneous findings. The disease causes extensive morbidity and frequently early mortality, and currently there is no specific and effective treatment. Most cases manifest at birth or shortly thereafter, and the signs and symptoms persist throughout life, having a significant clinical and psychological impact on patients and their families and also imposing an enormous burden on global healthcare systems.

DEBRA International is a coalition of over 40 national DEBRA groups, organizations that advocate on behalf of patients with EB and their families. They provide support to those impacted by the disease by disseminating information on EB and its devastating consequences and supporting research on this condition. Toward these goals, DEBRA organizes periodic meetings of basic researchers, physician-scientists, and clinicians involved in EB in different capacities. One of the premier national groups, DEBRA UK, organized The First Global Congress on EB, EB2020, in London on 20–24 January 2020. This comprehensive meeting brought together all interested parties, that is, scientists, clinicians, patients, and the pharmaceutical industry, to assess the state of research on all aspects of this complex disorder and provide a platform for dialogue to facilitate development of effective treatment and potential cure.

EB2020 was an unqualified success from the very beginning: over 700 participants from 54 countries registered to the meeting, which consisted of 115 platform presentations by 78 invited speakers, 138 electronic poster presentations, panel discussions, and conference debates (Figure 1). This Meeting Report summarizes the latest developments in EB research by highlighting novel findings that have formed the basis to advance the development of treatment and cure for this group of currently intractable disorders, as presented in EB2020.

Phenotypic spectrum and revised classification

EB was initially divided into three broad categories on the basis of the plane of blistering in the skin, as determined by immunofluorescence analysis and/or transmission electron microscopy. The three broad forms are (i) EB simplex (EBS), demonstrating intraepidermal blistering; (ii) junctional EB (JEB), with blistering within the dermal-epidermal basement membrane within the lamina lucida; and (iii) the dystrophic forms of EB (DEB), with blister formation below the lamina densa within the upper reticular dermis. Subsequently, the fourth subtype, Kindler syndrome, was identified with blistering at multiple levels within the skin (Fine et al., 2014).

Since the initial classification of EB into four broad subtypes, several subsequent modifications have been made, with the latest one published in 2020 as a result of a consensus meeting of an expert panel (Has et al., 2020a) (Table 1). The key points in this latest classification were the following: (i) elimination of eponyms with the exception of Kindler EB (previously known as Kindler syndrome); (ii) simplifying descriptions of clinical phenotypes within each subcategory; and (iii) categorization of different forms of EB as either classic or other skin fragility disorder. This distinction defined the classic forms as those with primary clinical findings consisting of blistering and erosions in association with mutations in 16 distinct genes. The other category includes conditions with blistering tendency, but the primary pathology and clinical manifestations are extracutaneous. This category is associated with mutations in five genes. Collectively, this latest revision in the classification clarifies several facets of EB and makes it more user-friendly for practicing clinicians.

Molecular genetics

A large number of sequence variants have been identified in the 21 skin fragility–associated candidate genes, with many of these defined as pathogenic or likely pathogenic, particularly the nonsense or frameshift mutations. A number of missense mutations, although segregating in the family and predicted to be damaging by bioinformatics programs, have been considered variants of unknown significance until proven to be functionally pathogenic.

The identification of mutations in EB genes in the early 1990s employed PCR-based amplification of individual

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Figure 1. The format of EB2020 included a number of innovations, including Congressional Debates. In this case, Dr John A. McGrath (standing right) is explaining his position on the complexity of EB as a current dilemma to other members of the panel, Drs Leena Bruckner-Tuderman, Johann Bauer, and Cristina Has, in front of the audience of over 700 participants. EB, epidermolysis bullosa.

exons, followed by manual Maxam and Gilbert or, later, automated Sanger sequencing. However, considering the multiplicity of EB-associated genes, some of which are exceptionally large and complex, this approach has proven to be time consuming and costly. Consequently, with the advent of next-generation sequencing technologies, contemporary mutation detection techniques include multigene arrays, such as those targeting different skin fragility–associated genes, or whole-exome sequencing and whole-genome sequencing. More recently, these approaches have been complemented with whole-transcriptome sequencing by RNA sequencing (RNA-Seq), which can provide critical additional information of the consequences of certain types of mutations (Saeidian et al., 2020). In fact, RNA-based transcriptome analysis by RNA-Seq provides the same information as DNA-based methods but, in addition, can yield information of consequences of the sequence variants at RNA level by visualization of splicing profiles (Sashimi plots) and gene expression levels (heatmap analysis). Both DNA- and RNA-based analyses allow variant detection and variant prioritization by bioinformatics toward mutation detection and also allow homozygosity mapping, particularly helpful for identification of candidate genes in consanguineous families.

The advances in mutation detection technologies raise the following question: why do we need to know mutations in EB? There are several reasons: First, the mutation information can be used for confirmation of diagnosis with subclassification as well as for prognostication of the severity and overall outcome of the disease in general terms. Furthermore, the mutation information can be used for carrier detection and genetic counseling, especially in consanguineous families who are at risk of recurrence of the disease. The knowledge of mutations also forms the basis for prenatal testing and preimplantation genetic diagnosis. Although prenatal testing is readily available through chorionic villus sampling, recent advances potentially allow determination of the fetal genotype noninvasively by sampling the mother's peripheral blood at the very early stages of pregnancy, and preimplantation genetic diagnosis allows exclusion of the disease even before the pregnancy starts. Finally, information on the specific mutations is a prerequisite for novel allele-specific treatments currently in development for EB in the realm of personalized medicine (described later).

Preclinical therapy development

Prospects of gene therapy. Progress in understanding the molecular genetics and pathomechanistic details leading to EB phenotypes, combined with availability of animal models, mostly transgenic mice, has allowed development of novel treatment modalities. A large number of different approaches have been tested at the preclinical level, and some have recently progressed to early clinical trials, predominantly focusing on patients with recessive DEB (RDEB). The treatment approaches are multiple, often complementary, varying from attempts to enhance wound healing and tissue regeneration to gene replacement and repair, protein replacement, and cell-based therapies (Dourado Alcorte et al., 2019; Marinkovich and Tang, 2019; Prodinger et al., 2019). Some therapies aim at permanent cure, whereas others may require a lifelong application for alleviation of the phenotypes by specifically, but temporarily, correcting the underlying genetic defects. Many of these approaches entail sophisticated, allele-specific treatment in the realm of personalized medicine. At the same time, some of these studies focus on improving QOL of affected individuals by counteracting symptoms such as itch and pain, as well as the sequelae of skin blistering, including scarring, infections, and development of highly metastatic squamous cell carcinomas (SCCs) (Has et al., 2020b).

Gene replacement. The gene therapy development for RDEB has largely focused on gene replacement approaches, particularly delivery of type VII collagen cDNA into the skin. One approach is direct topical gene delivery either by viral vectors such as herpes simplex virus (Krystal Biotech, Pittsburgh, PA) with epidermotropism, or by delivery into skin using a nonviral carrier such as a highly branched poly-β-ester polymer (Amryt Pharma PLC, Dublin, Ireland). The topically applied construct allows expression of type VII collagen in the skin and assembly of functional anchoring fibrils. In both cases, the transgene does not integrate into the recipient's genome, and continuous, perhaps lifelong, application for sustained benefits of the treatment is required. Early clinical trials are currently attempting to determine efficacy and the optimal frequency of treatment required.

Another approach to correct RDEB entails ex vivo methodologies where the patient's own cells are genetically corrected by incorporating *COL7A1* cDNA into the cells, followed by introduction of these cultured cells into the patients' skin. In one approach (Fibrocell Science/Castle Creek Biosciences, Exton, PA), autologous fibroblasts are corrected in culture, and these cells are then directly injected to the edges of wounds. In another (Abeona Therapeutics, New York, NY), autologous keratinocytes are corrected with a lentiviral vector, and corrected cells are then grown into epidermal sheets that can be grafted onto denuded areas of the patient's skin (Eichstadt et al., 2019). Another attempt to develop such skin grafts (GENEGRAFT) is to combine gene-corrected keratinocytes and fibroblasts into a skin equivalent that then can

Table 1. Revised 2020 Classification of EB with Mutated/Gene Protein Systems Associated with Each Subtype

Plane of Skin Cleavage	EB Type	Inheritance	Mutated Gene(s)	Affected Protein(s)
Classical types of EB[1]				
Intraepidermal	EB simplex	AD	*KRT5, KRT14*	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		AR	*KRT5, KRT14*	Keratin 5, keratin 14
			DST	Bullous pemphigoid antigen 230 (BP230) (syn. Dystonin)
			EXPH5	Exophilin-5
			PLEC	Plectin
			CD151	CD151 antigen (syn. Tetraspanin)
Lamina lucida	Junctional EB	AR	*LAMA3, LAMB3, LAMC2*	Laminin 332
			COL17A1	Tupe XVII collagen
			ITGA6, ITGB4	Integrin α6β4
			ITGA3	Integrin α3 subunit
Intradermal	Dystrophic EB	AD	*COL7A1*	Type VII collagen
		AR	*COL7A1*	Type VII collagen
Mixed	Kindler EB	AR	*FERMT1*	Fermitin family homolog 1
Other disorders with skin fragility[1]				
Peeling skin disorders				
Intraepidermal	Peeling skin disorders	AR	*TGM5*	Transglutaminase 5
			CSTA	Cystatin A
			CTSB	Cathepsin B
			SERPINB8	Serpin protease inhibitor 8
			FLG2	Filaggrin 2
			CDSN	Corneodesmosin
			DSG1	Desmoglein 1
			SPINK5	LEKTI
Erosive disorders				
Intraepidermal	Erosive skin fragility disorders	AR	*DSP*	Desmoplakin
			JUP	Plakoglobin
			PKP1	Plakophilin 1
			DSC3	Desmocollin 3
			DSG3	Desmoglein 3
Hyperkeratotic disorders with skin fragility				
Intraepidermal	Keratinopathic ichthyoses	AD	*KRT1, KRT10, KRT2*	Keratin 1, 10, 2
		AR	*KRT10*	Keratin 10
	Pachyonychia congenita	AD	*KRT6A, KRT6B, KRT6C, KRT16, KRT17*	Keratin 6A, 6B, 6C, 16, 17
Connective tissue disorder with skin fragility				
Dermal	Syndromic connective tissue disorder with skin fragility	AR	*PLOD3*	Lysyl hydroxylase 3

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EB, epidermolysis bullosa.
[1]Note the distinction between the classical form of EB and the other disorders of skin fragility.
Adapted from Has et al. (2020a).

be grafted to the patient's skin (Gaucher et al., 2020). In support of the latter approach is the recent demonstration that correction of both keratinocytes and fibroblasts, cell types that in normal skin synthesize type VII collagen, is required for optimal assembly of the anchoring fibrils (Supp et al., 2019).

In addition to RDEB, epidermal grafts have been successfully used to correct the underlying defect in JEB, with defects in the *LAMB3* gene (Hirsch et al., 2017). These grafts were made of a holocloned stem cell population that has ensured the longevity of the cells after transplantation. One patient with extremely severe JEB was successfully transplanted, and the skin grafts have retained their functionality well beyond a decade after transplantation.

Gene repair. Several studies have explored the potential of gene repair, including correction of the mutations by CRISPR/Cas9 editing technology. One of the limitations of this approach is that a large number of cultured cells for graft production are required, but this can be counteracted by the development of inducible pluripotent stem cells (iPSCs) that, after gene correction, can be differentiated into keratinocytes or fibroblasts and used for graft development (Uitto, 2019). In the case of EB, iPSCs can also be generated from skin areas manifesting revertant mosaicism, a form of natural gene therapy, where the mutations have spontaneously reversed manifesting as patches of normal-appearing skin. It should be noted that revertant mosaicism in skin diseases has been primarily documented in keratinocytes, but

revertant mosaic fibroblasts have also been identified in the skin of patients with RDEB (Twaroski et al., 2019).

Allele-specific therapies. The prerequisite for the development of allele-specific therapies for EB is the specific knowledge of the types and positions of the mutations within the mutant gene. One such approach aims at deletion of a specific exon harboring the deleterious mutation by application of antisense oligomers such that it leads to skipping of an exon, which is deleted in-frame (Rodrigues and Yokota, 2018). This approach is particularly applicable to *COL7A1* because, among the 118 exons of this gene, 107 of them are in-frame. These exons are also relatively small, and deletion of an exon harboring pathogenic mutations results in the synthesis of only a slightly shortened, but largely functional, type VII collagen (Bremer et al., 2019). Another example of the allele-specific treatment is an attempt to develop small molecular weight compounds that allow read-through of a premature termination codon (PTC) generated as a result of the mutation (Bremer et al., 2019). Such molecules facilitate the synthesis of full-length protein by replacing the stop codon with an amino acid (Atanasova et al., 2017; Lincoln et al., 2018). It should be noted that such read-through molecules override only pathogenic PTCs, and they do not read through the endogenous stop codon of translation because of the nucleic acid context and the organization of the gene.

Protein replacement therapy. Besides counteracting the consequences of the mutations at DNA and mRNA levels, attempts have been made to develop protein replacement therapy for RDEB. Specifically, preclinical studies demonstrated that recombinant type VII collagen intravenously injected into *Col7a1* knockout mice homed into the skin, enhancing wound healing and prolonging the lifespan of these mice (Woodley et al., 2013). Based on information derived from such studies, this approach is currently on the way to clinical application.

Cell-based therapies. Cell-based therapies have particularly focused on stem cells with the notion that they could home to the skin and be coached to synthesize basement membrane components to enhance the repair of the molecular defect. The pioneering approach of cell-based therapy consisted of allogeneic bone marrow transplantation (BMT), which showed early promise but carries a risk of complication with a high degree of mortality, especially when complete myoablative preparation of the recipient is used (Vanden Oever et al., 2018). Subsequently, reduced-intensity conditioning regimens have been tested, and administration of different non-hematopoietic stem cells, including human cord blood–derived unrestricted somatic stem cells or human placenta-derived stem cells have been tried. Post-transplant cyclophosphamide treatment has also been shown to establish immunological tolerance, and it has been suggested that low-intensity conditioning of recipients for BMT could be used to tolerize patients for allogeneic skin graft when taken from the same individual (Ebens et al., 2019).

Mesenchymal stem cells. The usefulness of mesenchymal stem cells (MSCs) for treatment of RDEB has been tested both by intradermal injection as well as by intravenous infusion, with clinical improvement initially reported in a limited number of patients. Infusion of MSCs into 10 children with RDEB revealed that, although very few adverse events were noted, there was no increase in type VII collagen content in the skin (Petrof et al., 2015). Rather, the perceived benefits such as reported better sleep of the family suggested that administration of MSCs may provide some improvement in QOL of the patients and their families. A similar trial of intravenous allogeneic MSCs injected into adults with RDEB showed a transient reduction in disease activity in eight out of 10 subjects tested, with significant reduction of itch (Rashidghamat et al., 2019). Again, only in one individual, there was a transient increase in type VII collagen in skin, and the benefits noted are likely to reflect mechanisms independent of type VII collagen synthesis, such as inflammatory modulatory activities of the MSCs.

Small molecular weight compounds. A number of compounds have been tested for specific forms of EB toward alleviation of the disease complications. One example is EBS with mutations in the *KRT5* and *KRT14* genes, associated with increased IL-1β expression, with consequences on blister formation. A small molecular weight compound, diacerein, is an inhibitor of IL-1β, and laboratory studies together with early clinical trials demonstrated significant reduction in blistering, suggesting its potential for the treatment of EBS (Wally et al., 2018). Betulin, another small molecular weight compound, isolated from birch bark, has been shown to enhance wound healing in EB following topical application (Oleogel-S10; Amryt Pharma, PLC). Enhancement of wound repair by this compound has been suggested to result from accelerated keratinocyte migration and control of inflammation during different phases of wound healing (Wally et al., 2018).

Clinical trials and relevant endpoints

Clinical trials. Preclinical EB research and early phase clinical trials are now leading to larger phase II/III trials but bring challenges for researchers, clinicians, pharma, and patients. Understanding what response to treatment is meaningful for the patient is essential, and patient-related outcome measures should be incorporated into study designs. Reducing the burden of trial participation, for example, by limiting numbers of skin biopsies or blood draws, not always requiring a placebo arm, and trial design for smaller numbers of patients, should enable greater engagement but needs regulatory authority acceptance.

Financial challenges of phase II/III trials are significant, particularly for bespoke, personalized therapies, such as gene editing or gene-corrected iPSCs. More generic, off-the-shelf products such as recombinant collagen VII or allogeneic cell-based therapies are still very expensive, and even clinical trials of repurposed relatively cheap drugs such as losartan can be costly. With so many different approaches reaching later stage clinical trials, prioritization of which to take forward is essential. Ethical considerations around whether investigative medicinal products will remain available to participants following a trial are important, and there may be concerns over access to and reimbursement for different therapies outside the clinical trial setting.

Beyond regulatory and financial considerations, challenges arise from rare disease trials where patient numbers are limited, particularly those that are well characterized phenotypically and genetically. In large, well-established EB centers, many patients will have already been recruited to trials, restricting those available for enrollment to new studies. Limited resources and patient numbers mean that the selection of therapies to reach later phase trials needs careful

consideration. Whereas some potentially curative treatments are being developed, others may offer disease control or symptomatic improvement. Although a cure might take longer to develop and need a more personalized and therefore expensive approach, treatment using, for example, repurposed drugs might be more achievable in the short to medium term. With the latter, targeting treatment early in life before many complications of EB, such as scarring, contractures, and anemia, have become established, would be optimal.

Endpoints of clinical trials. The development of meaningful endpoints for EB clinical trials is essential but has proven difficult to achieve. A number of scoring systems can capture the physical severity of EB and symptoms such as pain and itch (Loh et al., 2014; Moss et al., 2009; Schwieger-Briel et al., 2015); however, these tools have limitations. For example, not all objective tools can differentiate active disease from accrued damage, and comparison of different types of EB may be problematic as the physical features and symptoms experienced may vary considerably. Additionally, the natural history of different types of EB is variable. With vast complexity, possible features, and complications of each particular subtype of EB, without a deep understanding of the natural history, it can be impossible to identify what a meaningful response to a potential therapy might be. For an overview of the relevant issues, as articulated by the Food and Drug Administration, see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/epidermolysis-bullosa-developing-drugs-treatment-cutaneous-manifestations-guidance-industry.

Regulatory authorities need an understanding of the specific features of EB when approving endpoints for clinical trials. Whereas wound healing trials for conditions such as diabetic or pressure ulcers will usually examine one wound per individual and select time to wound closure or wound size reduction as a primary endpoint, this becomes challenging in EB where wounds are numerous and tend to be in a constant state of healing and breakdown. Other challenges arise when attempting to differentiate blistering or wounds over a target area of the body compared with total disease activity. Although problematic and complex, establishing robust and appropriate endpoints is essential as clinical trials in EB move into phase III where efficacy becomes the main focus.

Patient management

Itch and pain. Alongside research into novel curative or disease-modifying therapies, efforts are focusing on symptom relief and managing and preventing complications of different forms of EB. Itch and pain are both major issues in EB and have been identified as priorities particularly for patients and families. For itch, antihistamines, gabapentin, and pregabalin are generally ineffective, but newer therapies such as apremilast, dupilumab, serlopitant, and naltrexone may hold promise. A multifaceted approach to pain management combining opioid and nonopioid medications with nonpharmacological interventions and psychological support of patients and care providers is recommended. Identification of small fiber neuropathy in RDEB may be a potential avenue to develop topical neurotrophic factors to alleviate neuropathic pain as well as itch in EB (von Bischhoffshausen et al., 2017). Systemic or topical cannabinoids are also being explored for itch and pain management in EB, as well as topically for wound healing, and are currently the focus of early phase clinical trials (Schräder et al., 2019).

Wound healing. Wound healing and reducing wound bioburden are other priority areas in EB. Topical agents such as glucose peroxidase-lactoperoxidase gel have very broad antibacterial effects on biofilms, which may be beneficial in EB (Flen Health UK Ltd, London, United Kingdom). Hydrofiber dressings that sequester bacteria when applied to wounds have a bacteriostatic effect and are well tolerated in fragile EB wounds where they can also help with autolytic debridement (ConvaTec, Reading, United Kingdom). Another potential approach is through targeting quorum sensing, a mechanism that enables bacteria to coordinate and act together to form biofilms, thereby reducing bacterial virulence irrespective of bacterial resistance to antimicrobials (Mölnlycke Health Care, Gothenburg, Sweden).

Skin cancer. The development of aggressive SCCs in RDEB is one of the major challenges in management. Although surgery remains the main approach, newer, more effective therapies for locally advanced or metastatic disease are a pressing need. There is some positive emerging experience using immunotherapy with drugs such as cetuximab, pembrolizumab, nivolumab, and cemiplimab, as well as a clinical trial for patients with EB with the polo-like kinase inhibitor, rigosertib, on the basis of positive preclinical in vitro and xenograft work (Atanasova et al., 2019).

Extracutaneous manifestations. Other complications, such as anemia, oral and dental problems, esophageal strictures, nutritional compromise, airway involvement, contractures, and eye involvement, provide a significant burden for patients with EB, but a good quality, robust evidence base for treatments and interventions is generally lacking. The development of clinical best practice guidelines over recent years, supported by DEBRA International, has tackled some of these knowledge gaps by assembling professionals, patients, and caregivers to develop expert consensus to give practical guidance in areas including oral health, pain, cancer, wound care, foot health, psychosocial care, and occupational therapy, for example (Chan et al., 2019; Khan et al., 2020; Martin et al., 2019).

Access to specialized EB care can be challenging, especially in resource-poor settings or in geographically remote areas. Hub and spoke models to deliver multidisciplinary team care and telemedicine, either via live, synchronous appointments or through store and forward transmission of information and images to specialists, both have the potential to improve patient access in a low cost, accessible format.

Patient registries. A number of local or national registries of patients with EB have been established but may suffer from small enrollment and are therefore limited in the ability to collate patients that might be suitable for inclusion in clinical trials of natural history projects. Efforts to create an international EB registry rely on consensus between participants, an agreed minimal dataset, an appropriate technological platform, and suitable consent and general data protection considerations. However, despite challenges, work continues to enable establishment of an international registry for EB.

Natural history

In most severe forms of EB, disease severity increases over time as skin and organ damage accrues and secondary complications occur. For example, in severe RDEB, infants and toddlers tend

to thrive, but through the first decade, nutrition becomes compromised, growth falters, inflammation increases, and anemia develops. Later, chronic wounds, scarring, and further sequelae from inflammation manifest, and from around 20 years onward, SCC development and the other established morbidities become key. Children with RDEB deviate from standard growth curves early in life, from the age of 2 years on for weight and from 8 years on for height (Reimer et al., 2019). These findings highlight potential windows of opportunity to maximize clinical management, such as through early insertion of a gastrostomy tube. Further, as newer therapies are developed, especially those targeting inflammation or scarring, treating patients with EB before the onset of irreversible damage, that is, in early childhood, should be the aim.

Conclusions: Future prospects of research toward treatment and cure

EB2020 was an unqualified success in reviewing the state of the basic research on EB and related skin fragility disorders as well as drug development and patient management, projecting to the future. The meeting covered the basic science of the epidermis and cutaneous basement membrane zone, molecular genetics of EB with diagnostic and prognostic implications, and the breadth of preclinical treatment development leading to clinical trials. Over a dozen pharmaceutical companies are currently involved in development of new therapies, and at least three phase III clinical trials are at the early stages or will soon commence to test their products for efficacy in patients with EB. These developments clearly left the scientists and clinicians in this meeting with a palpable sense of enthusiasm with the hope that we are approaching breakthroughs toward phenotypic alleviation and possibly eventual cure in an expedited fashion. Such enthusiasm was matched by the patients and their families in the audience, and these developments on EB have been long anticipated by the patients. While being cautiously optimistic, patients have continued to express their appreciation of the scientists' work in the field. Such appreciation was eloquently expressed by Iñigo Ibarrando, a patient with EB participating in a research forum organized by DEBRA Spain in 2012: "Thank you note to the scientists: You are walking and building a path for people with EB, away from death or struggling for life…Thanks not only for walking this path with us, but also for us. Please keep walking."

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CONFLICT OF INTEREST

The authors of this Report served as Co-Chairs of the EB2020 Meeting.

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