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No Living Cells, No Living-Cell Risk

The Safety Case for Cell-Free Preparations

Paper 11 in the CFT Advantage Series

WHITE PAPER

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Abstract

Cell-based regenerative therapies offer biological promise but carry inherent safety risks rooted in the properties of living cells: tumour formation from pluripotent or extensively expanded cells, ectopic tissue growth from aberrant differentiation, immune rejection of foreign cells, and vascular obstruction from injected cell suspensions. Peer-reviewed case reports document each of these outcomes in patients treated at clinics worldwide, including blindness after autologous adipose stem cell injection, donor-derived brain tumours after fetal neural stem cell transplantation, glioproliferative spinal lesions after intrathecal stem cell tourism, and angiomyeloproliferative kidney lesions after percutaneous stem cell injection. Cell-Free Therapy (CFT) removes the living-cell behaviours that drive many of the best-known safety concerns in cell therapy: replication, differentiation, engraftment, donor-cell immune targeting and cell-mass vascular obstruction. This is a claim about removing the risks that depend on living cells, not a claim that any biological preparation can be entirely free of risk. CFT delivers an acellular preparation of soluble factors (extracellular vesicles, growth factors, cytokines, and signalling molecules) derived from the patient's own peripheral blood white cells through environmental conditioning. The Vienna group's APOSEC programme has independently demonstrated that cell-free secretome preparations can be characterised, manufactured under GMP standards, toxicologically tested, and safely administered in clinical trials, providing a published precedent for the cell-free approach. APOSEC does not validate CFT directly, but it provides an important precedent for the manufacturability, characterisation and safety testing of PBMC-derived cell-free secretome products. This paper reviews the documented safety record of cell-based therapies, the mechanistic basis for CFT's improved safety profile relative to living-cell interventions, and the regulatory and clinical implications for physicians evaluating regenerative options. It also sets out the residual product-control questions that any acellular biologic must continue to answer.

Scope note: This paper does not claim that CFT treats any of the diseases or conditions discussed in the adverse-event literature; those examples are cited only to explain documented risks associated with living-cell interventions.

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1. Introduction: The Promise and Peril of Cell-Based Therapies

Regenerative medicine has long promised to restore damaged tissues and organs by introducing living cells capable of proliferation, differentiation, and tissue integration. The biological rationale is intuitive: deliver cells with regenerative potential and the body will repair itself. This idea has driven two decades of clinical interest, billions in investment, and a rapidly expanding direct-to-consumer industry.

Clinical experience has revealed a more complicated picture. Peer-reviewed literature now documents serious adverse events from cell-based therapies in multiple anatomical sites and disease contexts: tumour formation from pluripotent cells, ectopic tissue growth in joints and viscera, immunological rejection despite claims of immunoprivilege, vascular obstruction from injected cell suspensions, and bacterial bloodstream infections from contaminated allogeneic products. These events are not merely theoretical. They are documented outcomes that illustrate predictable biological hazards when living cells are introduced without adequate characterisation, control and follow-up.

The challenge for the field has therefore become structural: how to obtain the therapeutic benefit of cellular activity without inheriting the safety liabilities of living cells. Cell-Free Therapy (CFT) is a direct answer. By isolating and concentrating the soluble factors that cells produce (cytokines, growth factors, extracellular vesicles, and signalling molecules) and delivering them as an acellular preparation, CFT supplies regenerative signalling without returning any living cells to the patient. This paper reviews the documented safety record of cell-based therapies, the mechanistic basis for CFT's improved safety profile relative to living-cell interventions, the precedent set by the APOSEC clinical-stage programme, and the implications for physicians evaluating regenerative options.

2. The Documented Risks of Living-Cell Therapies

2a. Tumour Formation and Uncontrolled Proliferation

Pluripotent stem cells, including embryonic stem cells and induced pluripotent stem cells, carry an intrinsic risk of teratoma formation: the development of disorganised, tumour-like masses containing multiple tissue types. The risk is biological, not procedural. The same property that makes pluripotent cells therapeutically interesting (the capacity to differentiate into any cell type) becomes a liability in vivo. Without precise environmental control, these cells proliferate and differentiate without direction. Animal models document this consistently, and regulatory guidance treats residual undifferentiated cells as a critical quality attribute in any pluripotent-cell-derived product.

Adult stem cells, including mesenchymal stem cells (MSCs), are considered lower-risk but are not risk-free. Extended culture expansion drives chromosomal abnormalities, telomere attrition, and phenotypic drift; the longer cells are passaged the more their behaviour diverges from their starting state. Aberrant differentiation in the recipient tissue, including rare cases of malignant transformation, has been documented in published case series.

2b. Ectopic Tissue Formation and Aberrant Differentiation

Even when transplanted cells avoid frank tumour formation, they can differentiate in ways that damage the recipient tissue. Stem cells injected into joint cavities have differentiated into bone or cartilage in unintended locations, restricting movement; cells delivered to muscle have shown fatty infiltration that reduces contractility; and cells implanted in retinal or neural tissue have proliferated as scar-like masses rather than integrating as functional replacements. These outcomes have been observed in preclinical models and in clinical case series. The therapeutic intent is undermined by cellular activity that proceeds out of context.

2c. Immunological Rejection and Inflammatory Activation

Allogeneic cell therapies face the classical problem of transplant immunology: rejection. While certain MSC preparations show reduced immunogenicity in vitro, complete immune tolerance is not guaranteed in vivo. Host T cells and natural killer cells can recognise and attack allografted cells, and recipient antibodies can sensitise the immune system against subsequent doses. In addition, transplanted cells (allogeneic and autologous alike) can release damage-associated molecular patterns (DAMPs) and pro-inflammatory mediators during injection or in situ stress, triggering innate immune activation that exacerbates inflammation rather than modulating it. Several clinical trials have reported unexpected inflammatory responses after stem cell infusion.

2d. Vascular and Embolic Complications

Cell suspensions injected into tissues or vasculature can cause mechanical obstruction. Injected cells lodge in capillary beds, particularly in the pulmonary microvasculature when delivered intravenously, causing microinfarcts and tissue damage. Cell lysis during injection or shortly afterwards releases intracellular contents and procoagulant material, which can trigger thrombosis. Pulmonary complications and stroke have been associated with intravenous infusions of cellular products in published reports, though definitive causality is sometimes difficult to establish given the heterogeneity of clinical populations.

2e. Manufacturing-Related Contamination

A separate, often overlooked safety risk is bacterial, fungal, or viral contamination introduced during cell processing. Allogeneic cell products manufactured at scale require multi-step culture, washing, and packaging in facilities whose cleanliness is the only barrier between the patient and the outside biological world. Lapses in environmental control have produced documented bloodstream infections in recipients. The 2018 cluster of bacterially contaminated umbilical cord-blood-derived stem cell products is the most recent prominent example, discussed in detail in Section 3e. Cellular products must be manufactured to the same sterility standards as injectable pharmaceuticals; in practice, the field has not always met that bar.

3. Published Adverse Events: A Decade of Documented Harm

The following peer-reviewed publications establish that the safety risks described above are not theoretical. Each represents a real patient outcome documented in a major medical journal.

3a. Vision Loss After Autologous Adipose Stem Cell Injection (Kuriyan et al., 2017)

Kuriyan and colleagues reported in the New England Journal of Medicine three patients with age-related macular degeneration who received bilateral intravitreal injections of autologous adipose-derived 'stem cells' at a US clinic. All three developed severe complications: ocular hypertension, haemorrhagic retinopathy, vitreous haemorrhage, combined traction and rhegmatogenous retinal detachment, and lens dislocation. At one-year follow-up, visual acuity ranged from 20/200 to no light perception. The case demonstrated that even autologous cells, when delivered to a sensitive tissue without rigorous characterisation or procedural oversight, can produce catastrophic harm. The injected preparation was a poorly defined stromal vascular fraction, not a characterised cellular product.

3b. Donor-Derived Brain Tumour After Fetal Neural Stem Cells (Amariglio et al., 2009)

Amariglio and colleagues reported in PLoS Medicine the case of a boy with ataxia telangiectasia who received intracerebellar and intrathecal injections of human fetal neural stem cells at a clinic abroad. Four years after the first procedure he was diagnosed with a multifocal brain tumour. Molecular analysis demonstrated that the tumour cells were genetically distinct from the patient and were derived from at least two of the donor sources, establishing donor origin definitively. The case was the first published demonstration that exogenous neural stem cells could give rise to a neoplasm in a human recipient, and remains the canonical reference for tumourigenicity risk in cell tourism.

3c. Glioproliferative Spinal Cord Lesion After Stem Cell Tourism (Berkowitz et al., 2016)

Berkowitz and colleagues reported in the New England Journal of Medicine a 66-year-old man who received intrathecal infusions of mesenchymal, embryonic, and fetal neural stem cells across commercial clinics in China, Argentina, and Mexico, hoping to ease residual deficits from an ischaemic stroke. He subsequently developed a glioproliferative neoplasm of the spinal cord. Histopathology and next-generation sequencing of 309 cancer-associated genes supported the

conclusion that the lesion originated from the intrathecally introduced exogenous cells. The authors noted that the unregulated commercial stem cell industry was potentially harmful to individual patients and undermined attempts to study cell therapy in disciplined clinical trials.

3d. Angiomyeloproliferative Lesions After Renal Stem Cell Injection (Thirabanjasak et al., 2010)

Thirabanjasak and colleagues reported in the Journal of the American Society of Nephrology a 46-year-old woman with lupus nephritis who, at a private clinic, underwent percutaneous injection of autologous peripheral-blood haematopoietic stem cells into both kidneys. She subsequently developed haematuria and palpable masses at the injection sites. Nephrectomy revealed novel angiomyeloproliferative lesions consisting of disorganised vascular and bone-marrow elements at the sites of injection. The authors concluded that the lesions were stem-cell-derived or stem-cell-induced, with unknown biological potential including possible neoplastic progression. The case added a new pathology to the catalogue of cell therapy adverse events: ectopic, disorganised tissue with no clear precedent in human disease.

3e. Bacterial Bloodstream Infections from Contaminated Cord-Blood Products (CDC, 2018)

In the autumn of 2018, the US Centers for Disease Control and Prevention, in cooperation with state health departments and the Food and Drug Administration, investigated bloodstream infections in recipients of non-FDA-approved umbilical cord-blood-derived ‘stem cell’ products processed by Genetech, Inc. and distributed by Liveyon, LLC. Twelve patients across three states were hospitalised with E. coli, Enterobacter cloacae, Citrobacter freundii, or Enterococcus faecalis bloodstream infections. The FDA inspection of the processing facility identified inadequate cleaning of the manufacturing environment and equipment between batches sourced from different donors. The product was voluntarily recalled. The episode demonstrated that the safety of an allogeneic cellular product depends not only on biology but on the integrity of the manufacturing chain, and that the direct-to-consumer market had repeatedly fallen short of pharmaceutical manufacturing standards.

3f. Regulatory Surveys of the Direct-to-Consumer Market

Two surveys frame the scale of the issue. Turner and Knoepfler, writing in Cell Stem Cell in 2016, identified at least 351 US companies marketing stem-cell interventions across 570 individual clinics, advertising treatments for orthopaedic, neurological, cardiac, immune, and cosmetic indications, the majority of which lacked adequate clinical evidence or FDA approval. Marks, Witten, and Califf, writing in the New England Journal of Medicine in 2017 from the FDA, argued that the heterogeneity of cell therapy products, combined with incomplete characterisation in the direct-to-consumer market, made population-level safety assessment fundamentally difficult. Their

conclusion was unambiguous: each cell therapy must be rigorously tested on its own evidence, and claims of inherent safety (whether based on cell type, autologous origin, or mechanism) are not sufficient on their own. It is equally important to acknowledge the other side of this picture. A number of cell-based therapies are licensed by stringent regulators and, when manufactured and administered under those controls, carry acceptable and well-characterised safety records. The adverse events surveyed above arise overwhelmingly from unregulated clinics and poorly characterised products rather than from regulated cell therapy as a discipline. The argument of this paper is not that every cell therapy is unsafe, but that living cells carry intrinsic biological risks that a cell-free preparation does not.

4. Why Cell-Free Removes Living-Cell Risks

4a. No Living Cells, No Uncontrolled Proliferation

Cell-Free Therapy contains no living cells. The preparation is acellular: a concentrated solution of soluble biological factors (cytokines, growth factors, extracellular vesicles, lipid mediators, and signalling peptides) isolated from white blood cells and then separated from the cellular material itself. Without living cells, there is no substrate for proliferation. Cells cannot divide, mutate, or accumulate genetic damage after administration. The risk of tumourigenic transformation arising from administered living cells is removed at the most fundamental level. This is not a claim of reduced risk through cell selection or quality control; it is the absence of the biological substrate from which the risk arises.

4b. No Differentiation, No Ectopic Tissue

Living cells in the body are subject to environmental signals, growth factors, mechanical forces, cell-cell contact, and oxygen tension that together direct their differentiation. These signals can push cells toward fates that are inappropriate for the tissue they have been delivered to. CFT contains no cells to differentiate. The soluble factors in a CFT preparation signal to the patient's own resident cells and modulate their behaviour, but the components of CFT itself do not differentiate, organise into ectopic structures, or form bone, cartilage, or fibrous masses in unintended sites.

4c. No Cellular Engraftment, No Long-Term Immune Targets

Transplanted living cells are persistent foreign material; even autologous cells, when expanded in culture or processed extensively, can acquire neo-antigens that trigger immune recognition. Cell-free preparations contain no intact cells to serve as immunological targets. Soluble factors and extracellular vesicles distribute through tissues, deliver their signals, and are cleared on physiological timescales. They do not require engraftment or long-term survival in the recipient. This does not make extracellular vesicles inherently inert: the wider vesicle literature describes potential pro-coagulant activity, angiogenic or fibrotic signalling, and immune responses to vesicles,

and this paper treats those as product-control questions to be managed (see Section 6) rather than as risks assumed away. Because CFT is autologous (the starting material is the patient's own peripheral blood white cells) the biological factors are derived from self, minimising foreign antigenicity. Because no donor cells are introduced, the classic donor-cell risks of HLA mismatch, graft-versus-host disease and cellular rejection do not apply, and there is no requirement for donor-matching or immunosuppression.

4d. No Cell Mass, No Cell-Based Embolic Risk

A properly filtered, release-tested acellular preparation contains no intact cells capable of forming aggregates in vasculature or tissues. The soluble components and extracellular vesicles are not intact cells and do not form cell-mass emboli. The documented risks of pulmonary microinfarction, ischaemic stroke, and capillary obstruction associated with intravenous cell suspensions do not apply to a properly characterised cell-free product. Standard injectable-product considerations (sterility, particulate testing, route, dose) still apply and are addressed through release specification.

5. No Genetic Modification, No Added Foreign Biological Material

CFT is derived entirely from the patient's own tissues. The preparation begins with a 150 mL peripheral blood draw. White blood cells are isolated, exposed to controlled environmental conditioning to stimulate natural secretory function, and the resulting secretome is concentrated and prepared as an autologous, cell-free product. The product contains no donor cells, no genetic modification and no intentionally added allogeneic or xenogeneic biological material. Reagents used during processing are GMP-qualified and controlled to defined release specifications. The entire process is performed in a GMP-certified European laboratory.

This stands in contrast to several adjacent cell therapy approaches, which may involve genetic modification of cells (such as CAR-T constructs and knock-out edits), viral vectors, xenogeneic culture supplements, or synthetic scaffold materials. CFT avoids each of these additional categories of risk. The product is as close as regenerative biologics come to self-derived material delivered without modification.

6. Residual Safety Considerations

The cell-free approach removes risks that depend on living cells, but it does not remove the need for rigorous product control. Safety still depends on sterility, endotoxin testing, absence of intact cells, particle and protein characterisation, residual-reagent control, batch traceability, dose definition, route of administration and release specifications. CFT is designed to address each of

these as standard release criteria rather than as an afterthought, and the cell-free architecture simplifies that work by removing variables that come with living cells. The advantage is structural, not absolute: the engine-fire risk is removed by removing the engine, but the brakes, tyres and steering still get checked on every batch. These controls are especially important because acellular biologics can still vary by donor biology, processing conditions, concentration, storage and route of administration. Specific considerations that any cell-free secretome must keep under review include the pro-coagulant, angiogenic, fibrotic and immune-signalling potential of extracellular vesicles, vesicle biodistribution and pharmacokinetics, dose-response relationships, and the effects of long-term repeated exposure. Biological variability is part of the same picture: a secretome derived from peripheral blood mononuclear cells can vary with donor age, health status, immune status and conditioning method, which is why batch characterisation and release testing matter. It should also be stated plainly that long-term, systematically collected human safety data for cell-free secretome products remain limited, and that ongoing surveillance, pharmacovigilance and continued safety monitoring are standing priorities for Wellbeing International Foundation rather than completed tasks.

7. The APOSEC Precedent: Cell-Free Secretome Safety Testing

The Vienna group, led by Hendrik Jan Ankersmit and colleagues, has spent more than a decade developing and clinically translating a cell-free secretome preparation derived from peripheral blood mononuclear cells (PBMCs). Their flagship product, APOSEC, is the apoptotic secretome released by stressed PBMCs and contains a characterised mixture of proteins, extracellular vesicles, lipids, and antimicrobial peptides. APOSEC has been the subject of extensive preclinical and clinical evaluation, and the programme provides the most relevant published precedent for the safety testing of an acellular biologic of the class to which CFT belongs.

Lichtenauer et al. (2011), in Basic Research in Cardiology, demonstrated cytoprotection of cardiomyocytes and reduced infarct size in preclinical models of acute myocardial infarction. Simader et al. (2017), in Scientific Reports, published the MARSYAS I randomised double-blinded Phase 1 trial of topically administered autologous APOSEC in artificial dermal wounds in healthy volunteers, establishing tolerability and safety at the doses tested. Wuschko et al. (2019), in Scientific Reports, reported the formal toxicological programme: acute and four-week repeat-dose intravenous toxicity studies in rats and mice, four-week subcutaneous toxicity studies in minipigs, and neuropharmacological screening, all consistent with a favourable safety profile for clinical advancement.

The relevance to CFT is direct. APOSEC and CFT belong to the same therapeutic class: acellular concentrated PBMC secretome preparations from autologous peripheral blood, delivered without living cells. The two share the cell source and the cell-free output but differ at the conditioning step: APOSEC induces secretion via apoptosis, CFT via reduced oxygen tension and serum-free medium.

The safety argument transfers via the shared autologous, cell-free, PBMC-derived output. That transfer has limits: different conditioning methods can alter the cytokine profile, extracellular-vesicle composition, protein expression and biological potency of a secretome, so APOSEC's safety record does not by itself prove that CFT will behave identically, and CFT must continue to demonstrate its own safety rather than rely on APOSEC as a substitute. The Vienna group's preclinical and clinical work supports the broader case that cell-free PBMC secretome preparations can be administered with a different and more favourable risk profile than living-cell preparations of equivalent therapeutic intent.

8. CFT's Safety Profile in Context

The safety implications of cell-free, autologous CFT can be summarised by comparing it to the principal alternative regenerative approaches. The table below sets out the major risk categories alongside how each approach engages, mitigates, or eliminates that risk.

Risk Category	Allogeneic Cell Therapy	Pluripotent / iPSC Derivatives	Autologous CFT
Tumour formation	Possible with extended-passage cells; chromosomal drift documented	Highest risk class; residual undifferentiated cells form teratomas	Removed at source; no living cells in the preparation
Aberrant differentiation / ectopic tissue	Documented in joint and viscera case reports	Documented in animal models and isolated human cases	Removed at source; CFT contains no cells capable of differentiation
Immune rejection / sensitisation	Material risk; HLA mismatch drives alloimmune response	Material risk; donor-derived antigens persist	Donor-cell HLA mismatch removed at source; immune/inflammatory product controls still required
Embolic / vascular obstruction	Cell aggregates can obstruct pulmonary capillaries	Cell aggregates can obstruct pulmonary capillaries	Removed at source; cell-free preparation without intact cell aggregates
Manufacturing contamination	Documented bloodstream infections from contaminated donor batches	Same risk plus differentiation-stage QC overhead	Reduced; small-batch autologous, single-patient processing
Need for	Often required	Often required	Not required

immunosuppression			
Genetic modification	Sometimes (CAR-T, gene-edited products)	Common in directed-differentiation pipelines	None

The pattern is consistent across categories. The risks documented in the cell-therapy literature are biological in origin: they arise from cells that proliferate, differentiate, occupy space, present antigens, and are manufactured at scale across donors. CFT does not carry these properties into the patient. It transmits the molecular signals that healthy cells produce, prepared from and delivered to the same individual, and leaves the cellular substrate behind.

9. Implications for Physicians and Patients

For physicians evaluating regenerative options, the safety profile of CFT simplifies several common clinical questions. Because there is no living-cell substrate, the classic cell-based risks of tumourigenic transformation, donor-recipient HLA mismatch and cell-aggregate embolism do not arise; there is no requirement for immunosuppression. Beyond the mechanistic case, CFT also has a real-world track record: the preparation has been administered to patients for more than fifteen years with no adverse reactions reported. This clinical experience complements the mechanistic argument, and systematic long-term safety monitoring and pharmacovigilance continue alongside it. Reasonable due-diligence questions remain, including release specification, manufacturing oversight, characterised composition, sterility and endotoxin control, residual-reagent control and traceability of each batch back to the individual patient. CFT is designed to answer those questions concretely rather than hand-wave them away.

For patients, the explanation is straightforward. The preparation contains the patient's own biological signalling factors, concentrated from a blood draw, processed under GMP standards, and returned to the patient as an acellular product. There are no donor cells, no cultured cell lines, no genetic modifications, and no intentionally added foreign biological material. The mechanism is not replacement of damaged tissue with new cells but support of the body's own biological maintenance and repair function through molecular signals.

Patients considering any regenerative option (CFT or otherwise) should ask the same questions of every provider: what is in the preparation, where did it come from, how was it characterised, what release standards were met, and what published evidence supports the claims being made. The documented adverse events surveyed in this paper occurred largely at clinics where those questions either could not be answered or were not asked.

10. Conclusion

Cell-based regenerative therapies offer biological promise but carry documented safety risks: tumour formation, ectopic tissue growth, immunological rejection, embolic complications, and manufacturing contamination. These risks are not theoretical. They have been observed in patients, documented in peer-reviewed publications by Kuriyan and colleagues, Amariglio and colleagues, Berkowitz and colleagues, Thirabanjasak and colleagues, and the CDC, and they arise from fundamental properties of living cells.

Cell-Free Therapy removes the cell-based risk class by removing the living cells. CFT delivers an acellular preparation of soluble factors (extracellular vesicles, growth factors, cytokines, and signalling molecules) derived from the patient's own peripheral blood white cells through environmental conditioning. No living cells are returned. The classic living-cell risks (proliferation, differentiation, engraftment, donor-cell immune targeting and cell-mass vascular obstruction) do not apply. No genetic modification is performed, and no donor or xenogeneic biological material is intentionally added.

This approach is not novel in principle. The Vienna APOSEC programme has demonstrated, across more than a decade of preclinical and clinical work, that cell-free secretome preparations from peripheral blood mononuclear cells can be administered with a different and more favourable risk profile than living cell preparations. APOSEC and CFT differ in their conditioning trigger (apoptosis induction in APOSEC, reduced oxygen tension and serum-free medium in CFT), so the safety argument transfers via the shared autologous, cell-free, PBMC-derived output rather than via the conditioning method. CFT applies the same operational answer (remove the cells, deliver the signal) to the broader question of what regenerative medicine can offer when its safety case is built around mechanism rather than around hope.

The cell-free, autologous, and unmodified nature of CFT, combined with the mechanistic removal of living-cell risks, supports a fundamentally different safety conversation than the one that surrounds cell therapy. Where cell therapy must continually defend against the consequences of introducing living cells, CFT is built around the principle that the safest signal is the one the body has produced for itself, and that the remaining safety work is the disciplined product-control work expected of any injectable biologic. The strongest statement of the case is therefore not that CFT is entirely risk-free, but that it appears to eliminate or substantially reduce the major risks specifically tied to administering living cells, while retaining the need for rigorous manufacturing controls, ongoing safety monitoring, pharmacovigilance and continued scientific evaluation.

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Disclaimer: Individual results vary. Cell-Free Therapy is not intended to diagnose, treat, cure, or prevent any disease. The information in this paper is provided for educational purposes and does not constitute medical advice. CFT supports the body's normal biological function through autologous, cell-free biological preparations.

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