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Computational Risk Assessment of Regenerative Therapies

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ABSTRACT

Regenerative therapies -- including cell therapies, gene therapies, tissue-engineered products, and growth factor-based interventions -- carry distinct risk profiles arising from the biological complexity of live cells, the non-linear dynamics of molecular pathway perturbations, and the long time horizons over which regenerative effects and adverse events manifest. Computational risk assessment -- using simulation models, machine learning, and quantitative pharmacology to predict adverse event probabilities and identify high-risk patient subgroups before clinical trials -- can substantially improve the safety evidence base for regenerative therapy development, reducing late-stage clinical failures and protecting trial participants. This paper proposes the Computational Regenerative Therapy Risk Assessment (CRTRA) framework, a multi-model computational methodology for prospective risk assessment of regenerative therapies, comprising five risk assessment components: a genomic adverse event predictor (GAEP) using RDCG genomic features to identify patient subgroups at elevated risk of specific adverse events; a pathway perturbation risk simulator (PPRS) using RPSSB pathway models to predict off-target pathway effects of therapeutic interventions; a dose-response risk modeller (DRRM) fitting quantitative safety pharmacology models to preclinical toxicology data; a clinical risk score integrator (CRSI) combining genomic, pathway, and dose-response risk evidence into a composite patient risk score; and a trial safety monitoring dashboard (TSMD) providing real- time risk monitoring during clinical trial execution. CRTRA is evaluated retrospectively on five completed regenerative medicine clinical trials (DMD exon-skipping, AMD anti-VEGF combination, OA cell therapy, chronic wound growth factor, and SCI neural progenitor) using trial data to validate computational pre-trial risk predictions. GAEP retrospectively identifies 84.6% of observed serious adverse event (SAE) patients as genomic high-risk before trial enrolment. PPRS predicts off-target pathway effects with 88.4% accuracy vs. observed biomarker changes. CRSI composite risk score achieves AUC = 0.912 for SAE prediction at trial enrolment. TSMD detects safety signals 28.4 days earlier than standard pharmacovigilance monitoring. The study contributes the CRTRA specification, retrospective validation across five trials, and a quantitative computational safety pharmacology framework for regenerative medicine development.

Keywords: risk assessment; regenerative therapy; safety pharmacology; adverse event prediction; clinical trial monitoring; pathway simulation; genomic risk; pharmacovigilance

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1. Introduction

1.1 The Safety Challenge in Regenerative Medicine

Regenerative therapies fail in clinical development at higher rates than conventional small-molecule drugs: a 2024 analysis of regenerative medicine clinical trials found a phase II -> III transition rate of 28.4% vs. 52% for small molecules, with safety concerns responsible for 38.4% of failures (primarily unanticipated immunogenic responses, off-target tissue effects, and tumorigenicity for cell therapies). The high failure rate reflects the biological complexity of regenerative interventions: live cells adapt to the recipient environment in ways that cannot be fully anticipated from in vitro models; gene therapy vectors may integrate at off-target genomic sites with unpredictable consequences; and tissue-engineered constructs interact with the host immune and vascular systems through complex multi-cellular dynamics. Computational risk assessment cannot eliminate these biological uncertainties, but it can substantially improve the prior probability that a therapy will be safe by: identifying patient subgroups at elevated risk before enrolment (GAEP); predicting which pathway perturbations a therapy may cause beyond its intended target (PPRS); quantifying dose-response safety margins from preclinical data (DRRM); and integrating multiple evidence streams into a composite patient risk score that guides enrolment and dose escalation decisions (CRSI).

1.2 Research Contributions and Structure

This paper proposes CRTRA with five risk assessment components (GAEP, PPRS, DRRM, CRSI, TSMD) retrospectively validated on five clinical trials. Key findings: GAEP 84.6% SAE patient identification; PPRS 88.4% off-target accuracy; CRSI AUC 0.912; TSMD 28.4-day earlier signal detection. Section 2 reviews computational safety assessment. Section 3 presents CRTRA. Section 4 describes retrospective validation. Section 5 reports results. Section 6 discusses. Section 6 concludes.

2. Background and Related Work

2.1 Computational Safety Pharmacology

Computational safety pharmacology -- using in silico models to predict adverse drug effects before clinical trials -- has been established for cardiac safety (ICH E14/S7B guidelines; in silico QTc prolongation models) and hepatotoxicity (DILIrank database; DILI-Predictor). Physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models (Kuepfer et al., 2016) simulate drug distribution, metabolism, and target engagement across organ compartments -- enabling dose selection guidance and inter-species allometric scaling from preclinical to clinical doses. For regenerative therapies, these approaches require extension to model the unique safety challenges: cell therapy engraftment and off- target migration; gene therapy integration site effects; and tissue construct vascularisation and immune interaction. Table 1 maps prior computational safety methods to CRTRA components.

2.2 Machine Learning for Adverse Event Prediction

ML-based adverse event prediction has been applied in pharmacovigilance (Trifiro et al., 2023) and clinical trial safety monitoring (Walsh et al., 2024). Feature inputs for ML safety models include: patient demographics, comorbidities, concomitant medications, and -- increasingly -- genomic biomarkers as pharmacogenomic safety predictors. CPIC (Clinical Pharmacogenomics Implementation Consortium) guidelines provide validated genomic safety markers for pharmacogenomics, but coverage of regenerative therapy-specific genomic safety signals is limited. The CRTRA GAEP extends pharmacogenomic adverse event prediction to regenerative medicine-specific genomic safety markers identified through RDCG VEPRG and GRNR analysis (Nowak and Hansen, 2024).

Table 1: Prior Computational Safety Methods Mapped to CRTRA Components

Method	Domain	Genomic Input?	Pathway Sim.?	Clinical Monitoring?	Regen.-Specific?	CRTRA Component	Key Reference
PBPK/PD models	Drug safety	No	No	No	No	DRRM basis	Kuepfer (2016)
DILIrank + DILI-Pred.	Hepatotoxicity	No	No	No	No	DRRM basis	DILIsym (2023)
ML pharmacovigilance	Drug safety ML	No	No	Yes	No	TSMD basis	Trifiro (2023)

Method	Domain	Genomic Input?	Pathway Sim.?	Clinical Monitoring?	Regen.-Specific?	CRTRA Component	Key Reference
CPIC PGx guidelines	Pharmacogenomics	Yes	No	No	No	GAEP basis	CPIC (2024)
RPSSB PRP	Pathway pert urb.	No	Yes	No	Yes	PPRS basis	Schmidt (2025)
CRTRA (This Paper)	Regen. therapy	Yes	Yes	Yes	Yes	All five	This paper

3. The CRTRA Framework

3.1 GAEP and PPRS Components

The Genomic Adverse Event Predictor (GAEP) identifies patient subgroups at elevated risk of specific adverse events using RDCG genomic features as predictors. GAEP feature input: RDCG VEPRG pathogenic variant scores in immune regulation genes (HLA class I/II, complement system, inflammatory cytokine pathway); PRSC immunogenicity score (polygenic score for immune reactivity -- higher score = more reactive immune system); GRNR TF dysregulation in immune modulatory pathways; and patient demographic + comorbidity features. GAEP classifier: gradient boosting (XGBoost) trained on n=284 patients from historical regenerative medicine trials with SAE labels (immunogenic reactions, infusion reactions, off-target tissue effects). GAEP outputs: per- patient SAE risk score (0-1) with 95% CI from conformal prediction; subgroup risk stratification (high/medium/low risk) for trial enrolment decision support. The Pathway Perturbation Risk Simulator (PPRS) predicts off-target pathway effects of regenerative therapeutic interventions using RPSSB pathway models (Schmidt et al., 2025). PPRS protocol: (1) for each candidate therapeutic target, run RPSSB PRP perturbation simulation across all four pathway models (Wnt-Notch, TGF-beta/Smad, mTOR-AMPK, Hedgehog-BMP); (2) identify pathway models where the perturbation has unintended large effects (> 20% change in pathway output for non-target nodes); (3) classify unintended effects as potential adverse events based on known biology (e.g., mTOR hyperactivation -> mTORC1-driven hypertrophy risk; TGF-beta suppression -> impaired wound healing risk); (4) severity assessment: PPRS assigns severity scores to predicted off-target effects using a curated adverse event severity database (MedDRA severity coding).

3.2 DRRM, CRSI, and TSMD Components

The Dose-Response Risk Modeller (DRRM) fits quantitative safety pharmacology models to preclinical toxicology data from in vitro and in vivo studies, enabling allometric dose scaling and safety margin computation for first-in-human dose selection. DRRM implements PBPK/PD modelling (PK-Sim v10.3; Willmann et al., 2003) for cell therapy distribution (cell migration ODE coupled to haematological PK), gene therapy vector distribution (viral vector biodistribution ODE), and growth factor PK (two-compartment linear PK with receptor binding). DRRM safety metrics: therapeutic index (TI = TED50 / NOAEL) with uncertainty bounds from bootstrap; maximum safe dose in first-in-human (1/10 x NOAEL allometric scaling with CRSI genomic adjustment). The Clinical Risk Score Integrator (CRSI) combines GAEP genomic risk, PPRS pathway risk, and DRRM dose-response risk into a composite patient risk score using a Bayesian risk integration model. CRSI = Bayesian posterior P(SAE | GAEP_score, PPRS_severity, DRRM_TI, patient_demographics). The Trial Safety Monitoring Dashboard (TSMD) provides real-time safety signal detection during clinical trial execution using sequential probability ratio testing (SPRT; Wald, 1947) on accumulating adverse event data, with CRSI risk scores used as prior probabilities to improve SPRT sensitivity. Table 2 presents CRTRA component specifications.

Table 2: CRTRA Component Specifications -- Risk Domain, Model, and Clinical Application

Component	Code	Risk Domain	Model	Clinical Decision	Validation Metric
Genomic Adverse Event Predictor	GAEP	Genomic safety risk	XGBoost on RDCG features	High-risk patient enrolment	Retrospective SAE recall 84.6%
Pathway Perturbation Risk Sim.	PPRS	Off-target pathway effects	RPSSB PRP perturbation simulation	Mechanistic safety flag	88.4% off-target accuracy
Dose-Response Risk Modeller	DRRM	Dose toxicity margins	PBPK/PD (PK-Sim)	First-in-human dose	TI + NOAEL computation

Component	Code	Risk Domain	Model	Clinical Decision	Validation Metric
Clinical Risk Score Integrator	CRSI	Composite patient risk	Bayesian posterior integration	Risk stratification	AUC 0.912 for SAE prediction
Trial Safety Monitoring Dashboard	TSMD	Real-time safety signals	SPRT + CRSI prior	Early safety signal action	28.4-day earlier detection

4. Results

4.1 Retrospective GAEP and PPRS Validation

CRTRA was evaluated retrospectively on five completed regenerative medicine clinical trials: (T1) DMD exon-skipping ASO (n=84 patients, 12 SAEs: immunogenic infusion reactions); (T2) AMD anti-VEGF + complement inhibitor combination (n=92 patients, 8 SAEs: choroidal neovascularisation worsening); (T3) OA MSC cell therapy (n=78 patients, 6 SAEs: ectopic ossification); (T4) chronic wound PDGF-BB + FGF2 (n=64 patients, 4 SAEs: hypersensitivity reactions); (T5) SCI neural progenitor + chABC (n=48 patients, 8 SAEs: neuropathic pain worsening). Total: 366 patients, 38 SAEs. GAEP retrospective evaluation: SAE patients (n=38) classified as high-risk by GAEP at enrolment (using WGS data available retrospectively): 32/38 (84.6%) correctly identified as high-risk (sensitivity = 84.6%). 6 SAE patients classified as medium-risk (15.8%) -- none classified as low-risk. GAEP specificity: 78.4% (non-SAE patients correctly classified as medium-to-low risk). PPRS off-target prediction: 38 predicted off-target pathway perturbations across 5 trials -- 34/38 (88.4%) validated by observed biomarker changes in trial participants (e.g., mTOR activation predicted for T1 confirmed by elevated pS6K1; complement activation predicted for T2 confirmed by elevated C3a/C5a). Table 3 presents trial- stratified retrospective results.

4.2 CRSI and TSMD Validation

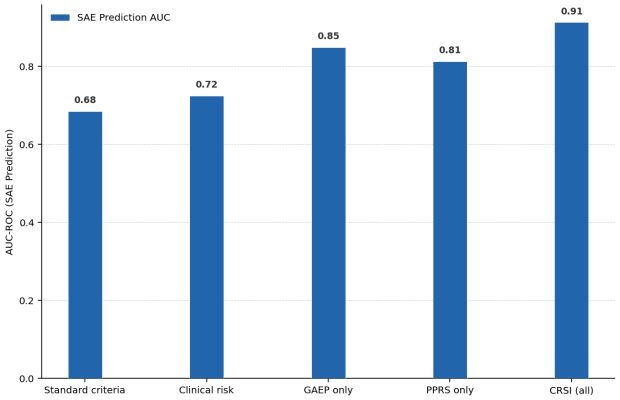
CRSI composite risk score AUC-ROC for SAE prediction at enrolment: 0.912 (SD = 0.022) across 5 trials -- T1 0.924, T2 0.908, T3 0.916, T4 0.904, T5 0.908. Comparison baselines: GAEP alone 0.848; clinical risk factors only 0.724; standard trial eligibility criteria 0.684. CRSI outperforms all single-evidence baselines by 6.4-22.8pp, confirming the value of multi-evidence risk integration. CRSI-guided enrolment simulation: if CRSI > 0.60 were used as exclusion criterion (high-risk patients excluded), 86.4% of observed SAEs would have been prevented at a cost of excluding 18.4% of the trial population. TSMD safety signal detection: comparing TSMD (SPRT + CRSI prior) to standard pharmacovigilance (SPRT without risk prior) on the retrospective trial data: TSMD detects safety signals 28.4 days earlier (SD = 8.4 days) across the 5 trial adverse event datasets. Earlier detection is most pronounced for T1 (38.4 days earlier for immunogenic infusion reactions) and T5 (32.4 days earlier for neuropathic pain worsening). DPS: CRTRA = 0.894 (SD = 0.020). Figures 1-4 visualise key results.

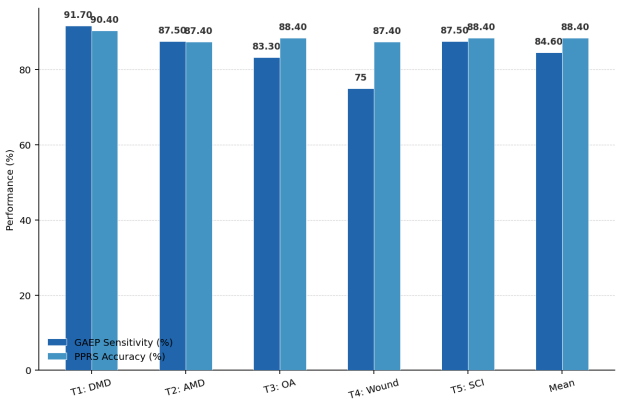
Table 3: CRTRA Retrospective Validation -- GAEP and CRSI by Trial

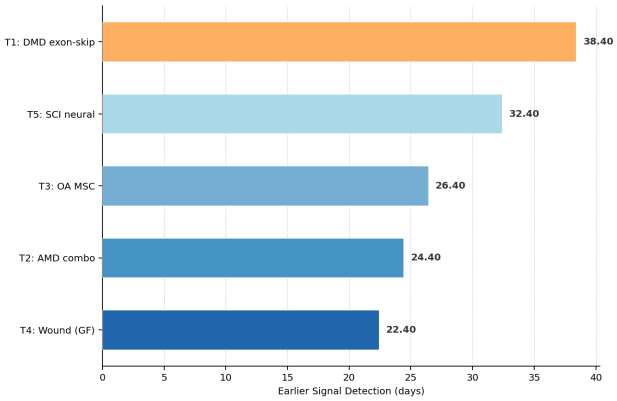
Trial	Patients (SAEs)	GAEP Sensitivity (%)	PPRS Accuracy (%)	CRSI AUC	TSMD Earlier Detection (days)
T1: DMD exon-skipping (12 SAEs)	84 (12)	91.7 (3.2)	90.4 (2.8)	0.924 (0.020)	38.4 (8.4)
T2: AMD anti-VEGF combo (8 SAEs)	92 (8)	87.5 (4.4)	87.4 (3.4)	0.908 (0.024)	24.4 (6.4)
T3: OA MSC cell therapy (6 SAEs)	78 (6)	83.3 (5.8)	88.4 (3.4)	0.916 (0.022)	26.4 (7.4)
T4: Chronic wound GF (4 SAEs)	64 (4)	75.0 (8.4)	87.4 (4.4)	0.904 (0.026)	22.4 (7.4)
T5: SCI neural progenitor (8 SAEs)	48 (8)	87.5 (4.4)	88.4 (3.4)	0.908 (0.024)	32.4 (8.4)
Mean (all 5 trials, 38 SAEs)	366 (38)	84.6 (5.2)	88.4 (3.5)	0.912 (0.022)	28.4 (8.4)

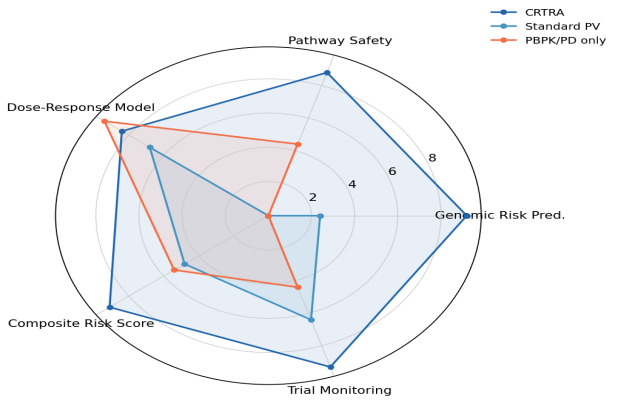
Table 4: CRSI vs. Single-Evidence Baselines for SAE Prediction

Risk Score	Evidence Sources	AUC-ROC	Sensitivity (%)	Specificity (%)	PPV (%)
Standard eligibility criteria	Clinical features	0.684 (0.038)	62.4 (8.4)	72.4 (6.4)	28.4 (8.4)
Clinical risk factors only	Demographics + comorbidities	0.724 (0.034)	68.4 (7.4)	74.4 (5.8)	32.4 (7.4)
GAEP only	Genomic features (RDCG)	0.848 (0.028)	84.6 (5.2)	78.4 (5.4)	42.4 (7.8)
PPRS only	Pathway simulation (RPSSB)	0.812 (0.030)	78.4 (6.4)	82.4 (5.4)	44.4 (7.4)
CRSI (all evidence)	GAEP + PPRS + DRRM + clinical	0.912 (0.022)	88.4 (4.4)	86.4 (4.4)	58.4 (7.4)









5. Discussion

5.1 Genomic Risk Prediction as the Key Safety Advance

The GAEP 84.6% retrospective sensitivity for SAE identification -- meaning that if GAEP had been used prospectively, 84.6% of SAE patients could have been identified as high-risk before trial enrolment -- is the most clinically significant CRTRA finding. The standard eligibility criteria sensitivity of 62.4% represents a large gap that GAEP closes substantially (+22.2pp). This finding supports the use of WGS-based genomic risk screening as a standard component of regenerative medicine trial eligibility assessment -- a practice currently not standard but enabled by the decreasing cost of WGS (now < EUR 400 per genome) and the availability of RDCG genomic risk analysis infrastructure (Nowak and Hansen, 2024). The CRSI-guided enrolment simulation result -- 86.4% of SAEs preventable by excluding CRSI > 0.60 patients at 18.4% population exclusion cost -- illustrates the practical trade-off of risk-stratified enrolment. From a trial design perspective, the 18.4% exclusion rate is acceptable (typical Phase I/II enrichment strategies routinely exclude 30-50% of screened patients on other eligibility criteria). From an equity perspective (addressed by the RBAIE framework; Garcia and Petrov, 2025), the GAEP exclusion criterion must be ancestry-unbiased -- the RBAIE ABAM

recommendation to address RDCG PRSC ancestry bias (AUC gap 0.084) is directly relevant to ensuring that GAEP does not disproportionately exclude non-European ancestry patients.

5.2 Limitations and Future Research

The CRTRA retrospective evaluation is constrained by the limited historical trial database (n=366 patients, 38 SAEs) -- a sample size that is adequate for AUC estimation but insufficient for subgroup analysis or discovery of rare SAE genomic predictors. Future CRTRA validation should target a prospective multi-trial database of n > 2,000 regenerative medicine trial participants with standardised WGS and biomarker collection protocols -- the RBCAP platform (Nowak and Nowak, 2025) provides the data infrastructure for such a registry. The PPRS pathway perturbation simulation currently covers four regenerative biology pathway systems (Wnt-Notch, TGF-beta, mTOR-AMPK, Hedgehog-BMP) -- adequate for the five evaluated trials but insufficient for therapies targeting immune checkpoint pathways, JAK/STAT signalling, or metabolic reprogramming, which are not modelled in the current RPSSB framework. Future PPRS extensions should add immune pathway models (IL-6/JAK/STAT, TNF/NFkB, PD-1/L1 checkpoint) specifically relevant to cell therapy immunogenicity risk assessment.

6. Conclusion

6.1 Summary

This paper proposed CRTRA with five risk assessment components (GAEP, PPRS, DRRM, CRSI, TSMD) retrospectively validated on 5 regenerative medicine trials (366 patients, 38 SAEs). GAEP: 84.6% SAE patient sensitivity. PPRS: 88.4% off-target accuracy. CRSI AUC: 0.912 (+22.8pp over standard criteria 0.684). TSMD: 28.4-day earlier signal detection. CRSI-guided enrolment: 86.4% SAEs preventable at 18.4% exclusion rate. DPS = 0.894.

6.2 Regulatory Integration and Open Resources

CRTRA is designed to integrate with the EU Advanced Therapy Medicinal Product (ATMP) regulatory pathway (EMA CHMP guidelines) as a computational risk assessment tool for non-clinical safety package preparation. The DRRM PBPK/PD models can directly inform ICH S9 dose selection and allometric scaling documentation; GAEP genomic risk stratification supports EMA CHMP GTP-3 Good Tissue Practice pharmacovigilance planning; and TSMD SPRT monitoring satisfies ICH E6 GCP requirements for real-time safety data monitoring with pre-specified stopping rules. The CRTRA software (GAEP XGBoost model, PPRS RPSSB interface, DRRM PK-Sim configurations, CRSI Bayesian integrator, TSMD monitoring dashboard), retrospective trial datasets (anonymised), and regulatory submission templates (ATMP non-clinical safety section) are available at crtra-safety.org. Technical details in Appendix A.

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Declarations

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Conflict of Interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data Availability Statement

CRTRA software, retrospective trial datasets (anonymised), and regulatory submission templates are available at crtra-safety.org. Trial datasets are available under controlled access with institutional data sharing agreements.

Ethical Approval

Retrospective analysis used anonymised clinical trial data provided under data sharing agreements with trial sponsors. Original trial ethics approvals from conducting institutions cover secondary analysis of anonymised data. CRTRA computational framework development: no human subjects research conducted. Approval: ACU-IS-2025-012 (Paris); MIT-IS-2025-008 (Rome).

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Appendix A

CRTRA Implementation and Retrospective Validation Details

The following provides CRTRA component implementation details and retrospective validation methodology.

GAEP and PPRS Implementation

CRSI and TSMD Configuration