Tier 1: Exploratory | Transcriptomic Isoform Splicing & Functional Genomics Calibration | Signal Rating: 2/5 Beakers | Nov 2, 2026

Alternative Splicing (PSI, Delta-PSI, Isoform Entropy & JSD) & BAGEL2/CERES CRISPR Essentiality Calibration: Native Rust vs. SciPy Across 12 Human Loci

Head-to-head calibration of effective-length-normalized Percent-Spliced-In (PSI, Delta-PSI, pooled Z_DeltaPSI), isoform usage Shannon entropy (H_iso), base-2 Jensen-Shannon divergence (JSD_iso), and copy-number-adjusted BAGEL2/CERES CRISPR-Cas9 log-Bayes factors (ln BF_gene, PP_ess) against SciPy v1.18.1 across 6 Development and 6 Untouched Reserve cohorts

Pathogenic mutations in core spliceosome factors (such as SF3B1 K700E and SRSF2 P95H) and RNA-binding proteins (such as TDP-43) rewire transcript isoform usage via poison-exon nonsense-mediated decay (NMD) and cryptic polyadenylation, creating selective cellular dependencies that can be mapped by genome-scale CRISPR-Cas9 knockout screens. Here we calibrate our native Rust 4-stage alternative splicing and Bayesian CRISPR essentiality solver -- implementing effective-length-normalized Percent-Spliced-In (Ψ , Delta Ψ , pooled Z DeltaΨ), isoform Shannon entropy (H iso) and base-2 Jensen-Shannon divergence (JSD iso), and BAGEL2 / CERES copy-number-corrected log-Bayes factors (ln BF gene , PP ess) -- against SciPy v1.18.1 across 12 human cohorts (6 Development and 6 Untouched Reserve, spanning 36 RNA-seq replicate pairs and 72 sgRNA guides). Native estimates reproduce SciPy v1.18.1 to 0.0000 mean absolute error with 100.0% regime concordance.

1. Biological & Mathematical Framework: Coupled Alternative Splicing & Bayesian CRISPR Essentiality

Evaluating whether an alternative splicing switch creates a functional cellular dependency requires coupling split-junction transcriptomic quantification with guide-level CRISPR-Cas9 dropout inference while guarding against focal copy-number amplification artifacts:

* Stage 1 -- Effective-Length-Normalized Percent-Spliced-In (Ψ , rMATS / SUPPA2 Formulation) & Differential Splicing (Delta Ψ): For cassette-exon, poison-exon, or mutually exclusive splicing events across R biological replicates in Condition 1 and Condition 2, inclusion split-junction reads I c,r span two splice junctions (effective mappable positions l I = 2(L read − 2 a anchor + 1)) whereas skipping reads S c,r span a single upstream-to-downstream junction (l S = L read − 2 a anchor + 1): Ψ c,r = (I c,r / l I) / (I c,r / l I + S c,r / l S) | Delta Ψ = Ψ̄ 1 − Ψ̄ 2 | Z DeltaΨ = Delta Ψ / √[p̂ (1 − p̂)(1 / N eff,1 + 1 / N eff,2)]

* Stage 2 -- Isoform Usage Shannon Entropy (H iso) & Base-2 Jensen-Shannon Divergence (JSD iso): Across all M expressed transcript isoforms of a locus with relative abundance vector p c = (p c ,1 , …, p c,M) and midpoint distribution m = 0.5(p 1 + p 2): H iso (p c) = − Sigma m =1.. M p c,m log 2 (p c,m) [bits] | JSD iso (p 1 ∥ p 2) = H iso (m) − 0.5 [H iso (p 1) + H iso (p 2)] calibrated directly against scipy.special.rel_entr

converted from nats to bits.

* Stage 3 -- Hart & Moffat (2016) BAGEL2 Log-Bayes Factor (ln BF gene) & Meyers et al. (2017) CERES Copy-Number DSB Guard: Given G independent sgRNA guides with raw log 2 fold-change x g and diploid copy-number ratio CN ratio = CN locus / 2 (applying the CERES double-strand-break shift x̃ g = x g + 0.145 max(0, CN ratio − 1) to remove Cas9 multi-cleavage G2/M arrest bias), log-Bayes factors are summed over core-essential N (u ess = −2.10, sigma ess = 0.65) and non-essential N (u non = −0.05, sigma non = 0.35) reference distributions: ln BF gene,CN-adj = Sigma g =1.. G [ln φ(x̃ g ; u ess , sigma ess) − ln φ(x̃ g ; u non , sigma non)] | PP ess = expit(ln BF gene,CN-adj + ln(pi 0 / (1 − pi 0)))

* Stage 4 -- Coupled Regime Classification & Negative-Control Reject Gate: Distinguishes synthetic-lethal splice switches (SpliceSwitchSyntheticLethalEssential), lineage-restricted or post-mitotic neuronal cryptic-exon pathologies (PathogenicExonSkippingOrCrypticInclusion), constitutive spliceosome core scaffolds (ConstitutiveCoreEssentialSplicingFactor), housekeeping safe-harbor controls (DEV-06 , rated 0), and focal copy-number amplification Cas9 DSB artifacts (RES-06 8q24.21 PVT1 18-copy amplicon, rated 0).

Signal Rating Assessment (2 Technical Validation -- Tier 1: Exploratory): This study is classified as a Tier 1: Exploratory head-to-head tool calibration benchmark and earns a 2 Technical Validation rating. It evaluates 12 human alternative splicing and CRISPR cohorts (6 Development + 6 Untouched Reserve, totaling 36 RNA-seq replicate pairs and 72 sgRNA guides) plus 2 deliberate 0 negative controls, achieving 0.0000 MAE against SciPy v1.18.1 .

2. Validation Dataset & Cohort Provenance (VAL-SET-020-SPLICING-CRISPR-12COHORT)

Effective junction length ratios (l I / l S = 2.0), BAGEL2 Gaussian hyper-parameters (u ess = −2.10, sigma ess = 0.65; u non = −0.05, sigma non = 0.35; pi 0 = 0.10), and the CERES copy-number slope (0.145 log 2 FC per extra diploid copy) were frozen on six Development cohorts (DEV-01 through DEV-06) and tested out-of-sample on six Untouched Reserve cohorts (RES-01 through RES-06):

| Cohort ID | | Validation Split | | Gene & Chromosomal Locus | | Alternative Splicing Event | | Disease or Cellular Context | | RNA Reps | | sgRNAs | | CN Ratio | | Primary Literature Anchor |

| DEV-01 | | Development | | BRD9 (5p15.33, SF3B1-K700E) | | Poison Exon 14a Cryptic 3′ss Inclusion (NMD) | | SF3B1-Mutant Uveal Melanoma & MDS | | 3 | | 6 | | 1.0 | | Inoue et al. (2019) Nature [1] |

| DEV-02 | | Development | | SMN2 (5q13.2 SMA) | | Exon 7 C840T Skipping vs. ISS-N1 ASO Rescue | | Spinal Muscular Atrophy Motor Neurons | | 3 | | 6 | | 1.0 | | Hua et al. (2008) AJHG; Finkel et al. (2017) NEJM [2] |

| DEV-03 | | Development | | PKM (15q23 PKM1/PKM2) | | Mutually Exclusive Exon 9 vs. Exon 10 Switch | | Glioblastoma & Lung Adenocarcinoma Glycolysis | | 3 | | 6 | | 1.0 | | Christofk et al. (2008) Nature [3] |

| DEV-04 | | Development | | UNC13A (19p13.11 ALS/FTD) | | Intron 20-21 Cryptic Exon Inclusion (TDP-43 Loss) | | Human iPSC Cortical & Spinal Motor Neurons | | 3 | | 6 | | 1.0 | | Brown et al. (2022) Nature; Ma et al. (2022) Nature [4] |

| DEV-05 | | Development | | BCL2L1 (20q11.21 Bcl-xL/xS) | | Exon 2 Distal vs. Proximal 5′ss Switch | | Colorectal & NSCLC Carcinoma Survival | | 3 | | 6 | | 1.0 | | Boise et al. (1993) Cell; Moore et al. (2010) Cell [5] |

| DEV-06 | | Development | | GAPDH / AAVS1 (Null Control) | | Constitutive Exon 5-7 & Safe-Harbor Control | | Isogenic Diploid RPE1 Baseline Control (0) | | 3 | | 6 | | 1.0 | | Hart et al. (2015) Cell [6] |

| RES-01 | | Untouched Reserve | | WRN (8p12 RecQ Helicase) | | Exon 4-5 Helicase Isoform Usage in MSI-H | | MSI-H Colorectal & Endometrial Cancer | | 3 | | 6 | | 1.0 | | Chan et al. (2019) Nature; Behan et al. (2019) Nature [7] |

| RES-02 | | Untouched Reserve | | EZH2 (7q36.1, SRSF2-P95H) | | CCNG Poison Exon 9.5 Inclusion (NMD) | | SRSF2-Mutant CMML & Acute Myeloid Leukemia | | 3 | | 6 | | 1.0 | | Kim et al. (2015) Cancer Cell [8] |

| RES-03 | | Untouched Reserve | | STMN2 (8q21.13 Stathmin-2) | | Intron 1 Cryptic Exon 2a Polyadenylation | | ALS Spinal Motor Neurons (Axonal Outgrowth) | | 3 | | 6 | | 1.0 | | Klim et al. (2019) Nature Neuroscience [9] |

| RES-04 | | Untouched Reserve | | CD19 (16p11.2 CART-19 Escape) | | SRSF3-Depleted Exon 2 Skipping (Deltaex2) | | Relapsed Pediatric B-Cell ALL | | 3 | | 6 | | 1.0 | | Sotillo et al. (2015) Cancer Discovery [10] |

| RES-05 | | Untouched Reserve | | PRPF8 (17p13.3 Core U5 snRNP) | | Constitutive Exon 38-39 RNase-H/Jab1 Core | | Pan-Cancer Core Essential Spliceosome Scaffold | | 3 | | 6 | | 1.0 | | Hart et al. (2015) Cell; Galej et al. (2013) Nature [11] |

| RES-06 | | Untouched Reserve | | PVT1 (8q24.21 CN=18 Decoy) | | Non-Coding Exon 3-4 in 18-Copy Amplicon | | 8q24-Amplified Line (Cas9 Multi-DSB Decoy, 0) | | 3 | | 6 | | 9.0 | | Meyers et al. (2017) Nature Genetics [12] |

Generated by: Native 3D Chromatin Graph Laplacian, TAD Insulation & RNA Phase-Separation Scaffolder Engine * Native 4-Stage Alternative Splicing (rMATS/SUPPA2 PSI + Isoform Entropy) & BAGEL2/CERES CRISPR Essentiality Engine

3. Quantitative Calibration Summary: Native Rust vs. SciPy v1.18.1

Across all 12 cohorts (36 RNA-seq biological replicate pairs and 72 sgRNA guides), the native Rust 4-stage splicing and CRISPR essentiality solver reproduces SciPy v1.18.1 (scipy.stats.norm.logpdf , scipy.special.rel_entr , and scipy.special.expit) to 0.0000 mean absolute error while executing in 0.2232 ms compared to 2.6852 ms for SciPy (a 12.03x speedup):

| Calibration Metric | | Development Split (n = 6) | | Untouched Reserve (n = 6) | | Combined 12-Cohort Benchmark | | Calibration Gate Threshold | | Gate Status |

| Differential Splicing |Delta(DeltaΨ)| MAE | | 0.0000 | | 0.0000 | | 0.0000 | | <= 1.0 x 10 −6 | | PASS (Exact) |

| Pooled Binomial Splicing |DeltaZ DeltaΨ | MAE | | 0.0000 | | 0.0000 | | 0.0000

| | <= 1.0 x 10 −6 | | PASS (Exact) |

| Isoform Usage Jensen-Shannon Divergence |DeltaJSD iso | MAE | | 0.0000 bits | | 0.0000 bits | | 0.0000 bits | | <= 1.0 x 10 −6 bits | | PASS (Exact) |

| BAGEL2/CERES Copy-Number-Adjusted |Deltaln BF gene | MAE | | 0.0000 | | 0.0000 | | 0.0000 | | <= 1.0 x 10 −5 | | PASS (Exact) |

| Posterior Essentiality Probability |DeltaPP ess | MAE | | 0.0000 | | 0.0000 | | 0.0000 | | <= 1.0 x 10 −6 | | PASS (Exact) |

| Coupled Splicing-CRISPR Regime Concordance | | 100.0% (6/6) | | 100.0% (6/6) | | 100.0% (12/12) | | 100.0% | | PASS (12/12) |

| Total Execution Runtime (12 Cohorts, 72 sgRNAs) | | 0.1116 ms | | 0.1116 ms | | 0.2232 ms (vs. 2.6852 ms SciPy) | | Speedup >= 5.0x | | PASS (12.03x) |

Generated by: Native 4-Stage Alternative Splicing (rMATS/SUPPA2 PSI + Isoform Entropy) & BAGEL2/CERES CRISPR Essentiality Engine * SciPy v1.18.1 (scipy.stats.norm.logpdf, scipy.special.rel_entr & scipy.special.expit)

4. Per-Cohort Alternative Splicing (Ψ , Delta Ψ , H iso , JSD iso) & BAGEL2/CERES CRISPR Comparison

Table 3 presents the complete head-to-head comparison across all 12 cohorts. Notably, the coupled solver separates: (1) synthetic-lethal splice switches in proliferating tumor cells (DEV-01 BRD9 , DEV-02 SMN2 , DEV-03 PKM , DEV-05 BCL2L1 , RES-01 WRN , and RES-02 EZH2 , where |Delta Ψ | = 0.5317-0.6709 and ln BF CN-adj = +85.98 to +131.20), (2) pathogenic exon-skipping or cryptic-exon events in post-mitotic motor neurons or immunotherapy-escape blasts where standard proliferation CRISPR dropout is negative (DEV-04 UNC13A , RES-03 STMN2 , and RES-04 CD19 , where |Delta Ψ | = 0.5599-0.7119 and JSD iso = 0.3398-0.4761 bits, while ln BF CN-adj < −27.0), and (3) the RES-06 8q24.21 PVT1 18-copy amplicon decoy where raw guide dropout looks falsely essential (ln BF raw = +25.0596) until CERES copy-number correction shifts ln BF CN-adj to −32.9166:

| Cohort ID | | Native Ψ 1 | | Native Ψ 2 | | Native DeltaΨ | | SciPy DeltaΨ | | Z DeltaΨ | | H iso,1 (bits) | | Native JSD iso | | SciPy JSD iso | | Raw ln BF | | Native ln BF CN | | SciPy ln BF CN | | PP ess | | Coupled Regime Classification |

| DEV-01 | | 0.6790 | | 0.0692 | | 0.6098 | | 0.6098 | | 2.6716 | | 1.1640 | | 0.3377 | | 0.3377 | | 102.8119 | | 102.8119 | | 102.8119 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| DEV-02 | | 0.1800 | | 0.8407 | | -0.6607 | | -0.6607 | | -2.9785 | | 0.9107 | | 0.3534 | | 0.3534 | | 122.9770 | | 122.9770 | | 122.9770 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| DEV-03 | | 0.8604 | | 0.1896 | | 0.6709 | | 0.6709 | | 3.1700 | | 0.6892 | | 0.3682 | | 0.3682 | | 89.5401 | | 89.5401 | | 89.5401 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| DEV-04 | | 0.5800 | | 0.0201 | | 0.5599 | | 0.5599 | | 2.4322 | | 1.2300 | | 0.3398 | | 0.3398 | | -28.6176 | | -28.6176 | | -28.6176 | | 0.0000 | |

PathogenicExonSkippingOrCrypticInclusion |

| DEV-05 | | 0.8217 | | 0.2621 | | 0.5596 | | 0.5596 | | 2.5819 | | 0.8176 | | 0.2511 | | 0.2511 | | 85.9842 | | 85.9842 | | 85.9842 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| DEV-06 | | 0.9603 | | 0.9569 | | 0.0034 | | 0.0034 | | 0.0420 | | 0.2747 | | 0.0005 | | 0.0005 | | -34.3303 | | -34.3303 | | -34.3303 | | 0.0000 | | NullHousekeepingIsoformNoiseControl (0) |

| RES-01 | | 0.8827 | | 0.3199 | | 0.5628 | | 0.5628 | | 2.6361 | | 0.6267 | | 0.2567 | | 0.2567 | | 131.1959 | | 131.1959 | | 131.1959 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| RES-02 | | 0.6206 | | 0.0889 | | 0.5317 | | 0.5317 | | 2.4710 | | 1.2199 | | 0.2585 | | 0.2585 | | 90.3406 | | 90.3406 | | 90.3406 | | 1.0000 | | SpliceSwitchSyntheticLethalEssential |

| RES-03 | | 0.7412 | | 0.0294 | | 0.7119 | | 0.7119 | | 3.2234 | | 1.0104 | | 0.4761 | | 0.4761 | | -27.7504 | | -27.7504 | | -27.7504 | | 0.0000 | | PathogenicExonSkippingOrCrypticInclusion |

| RES-04 | | 0.2204 | | 0.9110 | | -0.6906 | | -0.6906 | | -3.2167 | | 1.0653 | | 0.3952 | | 0.3952 | | -32.6679 | | -32.6679 | | -32.6679 | | 0.0000 | | PathogenicExonSkippingOrCrypticInclusion |

| RES-05 | | 0.9502 | | 0.9371 | | 0.0131 | | 0.0131 | | 0.1441 | | 0.3825 | | 0.0015 | | 0.0015 | | 162.8149 | | 162.8149 | | 162.8149 | | 1.0000 | | ConstitutiveCoreEssentialSplicingFactor |

| RES-06 | | 0.5193 | | 0.5040 | | 0.0153 | | 0.0153 | | 0.0685 | | 1.4169 | | 0.0003 | | 0.0003 | | 25.0596 | | -32.9166 | | -32.9166 | | 0.0000 | | OffTargetCopyNumberAmplificationArtifactReject (0) |

Generated by: Native GFA Pangenome Graph Topology, Residue-Interaction Network (RIN) & Cryptic Cavity Engine * Native 4-Stage Alternative Splicing (rMATS/SUPPA2 PSI + Isoform Entropy) & BAGEL2/CERES CRISPR Essentiality Engine * SciPy v1.18.1 (scipy.stats.norm.logpdf, scipy.special.rel_entr & scipy.special.expit)

5. Focal Splice-Junction & Copy-Number-Adjusted CRISPR Profile

Below we render the 12-cohort splicing-essentiality profile and focal exon-junction/sgRNA decomposition across DEV-01 (SF3B1 -K700E BRD9 poison exon 14a), RES-03 (STMN2 cryptic exon 2a in TDP-43 -depleted motor neurons), and RES-06 (8q24.21 PVT1 18-copy amplicon Cas9 DSB decoy):

Generated by: Native GFA Pangenome Graph Topology, Residue-Interaction Network (RIN) & Cryptic Cavity Engine * Native 4-Stage Alternative Splicing (rMATS/SUPPA2 PSI + Isoform Entropy) & BAGEL2/CERES CRISPR Essentiality Engine

Discussion & Key Takeaways

1. Exact Numerical Parity Across Splicing Quantification & Bayesian CRISPR Essentiality: Across all 12 human cohorts (36 RNA-seq replicate pairs and 72 sgRNA guides), our native Rust solver matches SciPy v1.18.1 (scipy.stats.norm.logpdf ,

scipy.special.rel_entr , and scipy.special.expit) to 0.0000 mean absolute error across Delta Ψ , Z DeltaΨ , isoform JSD iso , and copy-number-adjusted BAGEL2 log-Bayes factors, with 100.0% regime concordance and a 12.03x execution speedup.

2. Coupling Delta Ψ with BAGEL2 Separates Cell-Autonomous Lethality from Post-Mitotic & Immune-Escape Isoform Switches: Integrating transcriptomic isoform divergence (JSD iso) with CRISPR essentiality distinguishes splice switches that directly ablate cell viability (such as SF3B1 -K700E BRD9 poison exon 14a and SRSF2 -P95H EZH2 poison exon 9.5) from pathogenic isoform switches whose primary phenotype is neuronal axonopathy (UNC13A , STMN2) or chimeric antigen receptor epitope loss (CD19 Deltaex2).

3. Bioinformatics Scope & Guarding Against Copy-Number Cas9 Toxicity: Computational splicing and CRISPR dependency analyses identify statistical correlations and candidate functional exons rather than direct clinical efficacy. Incorporating CERES copy-number normalization inside the Bayesian essentiality engine prevents focal oncogene amplicons (such as 8q24.21 MYC/PVT1) from generating false-positive essentiality calls due to Cas9-induced double-strand-break toxicity.

NCBI RefSeq / GENCODE / DepMap Provenance Ledger

| Accession ID | | Gene / Locus | | Canonical & Alternative Isoform Architecture | | Functional Consequence | | Database Verification |

| NM_023924.5 | | BRD9 (5p15.33) | | Exon 14-15 canonical vs. SF3B1-K700E cryptic 3′ss poison exon 14a | | Premature stop codon triggers NMD and disrupts non-canonical BAF chromatin remodeling | | NCBI RefSeq & DepMap Verified |

| NM_017411.4 | | SMN2 (5q13.2) | | Exon 7 C840T exonic splicing enhancer loss vs. ISS-N1 ASO inclusion | | Exon 7 skipping yields unstable SMNDelta7 protein; ASO restores full-length SMN | | NCBI RefSeq & ClinVar Verified |

| NM_002654.6 | | PKM (15q23) | | Mutually exclusive Exon 9 (PKM1) vs. Exon 10 (PKM2) | | PTBP1/hnRNPA1-driven Exon 10 inclusion enables FBP-allosteric Warburg glycolysis | | NCBI RefSeq & GENCODE Verified |

| NM_001080421.3 | | UNC13A (19p13.11) | | Intron 20-21 128-bp cryptic exon upon nuclear TDP-43 depletion | | Frameshift NMD ablates synaptic vesicle priming protein in ALS/FTD neurons | | NCBI RefSeq & GWAS Catalog Verified |

| NM_000553.6 | | WRN (8p12) | | Exon 4-5 exonuclease and Exon 14-21 RecQ ATPase helicase core | | Synthetic lethal dependency in MMR-deficient MSI-H expanded (TA) n repeats | | NCBI RefSeq & DepMap Verified |

| NM_004456.5 | | EZH2 (7q36.1) | | SRSF2-P95H CCNG motif-driven poison exon 9.5 inclusion | | Triggers NMD of PRC2 H3K27 methyltransferase in myelodysplastic/CMML clones | | NCBI RefSeq & COSMIC Verified |

| NM_007029.4 | | STMN2 (8q21.13) | | Intron 1 cryptic exon 2a splice acceptor and premature poly(A) site | | Truncates stathmin-2 microtubule regulator upon TDP-43 loss in ALS motor neurons | | NCBI RefSeq & GENCODE Verified |

| NM_001770.6 | | CD19 (16p11.2) | | SRSF3-regulated Exon 2 cassette skipping

(Deltaex2 isoform) | | Eliminates extracellular FMC63 CAR-T binding epitope while retaining membrane anchor | | NCBI RefSeq & GENCODE Verified |

Generated by: NCBI Entrez E-Utilities * CRV Science Labs PoliteCacheManager * Native Codon dN/dS, Selection Relaxation (RELAX k) & Trait-Loss Engine * Native 3D Chromatin Graph Laplacian, TAD Insulation & RNA Phase-Separation Scaffolder Engine * Native Somatic Coalescent, 96-Channel Mutational JSD, NNLS COSMIC Deconvolution & Synthetic Lethality Engine * Native 4-Stage Alternative Splicing (rMATS/SUPPA2 PSI + Isoform Entropy) & BAGEL2/CERES CRISPR Essentiality Engine

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