# New FDA guidance on Genome Editing Safety Standards

## IDT has you covered

- Customized on-and-off-target analysis **from the team who performed the safety assessment for the first personalized mRNA-based therapy** with personalized intake and project calls
- **Genome-wide, cell-based off-target nomination** for Cas9 and Cas12 editing systems with UNCOVERseq™ (unbiased discovery) with well-characterized positive control
- **High-sensitivity confirmation** identifying true positives down to 0.01% editing using targeted deep sequencing with rhAmpSeq™ (on- and off-target quantified together; >50,000x typical depth), including translocation analysis
- **Variant-aware analysis** layered in via *in silico* supplementation incorporating variants from HGDP and gnomAD
- **Transparent, regulatory-ready reporting** personalized, annotated reports & consultations with genomic context, risk narrative, and full NGS/bioinformatics transparency & guidance

## UNCOVERseq™ has an industry leading balance of sensitivity and precision

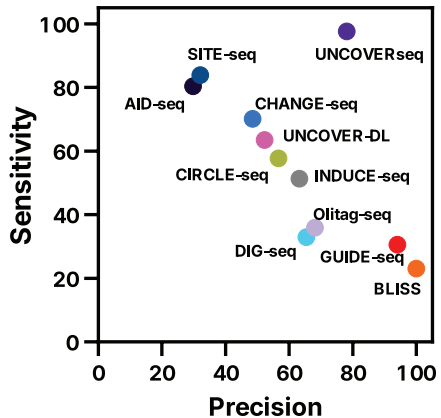


**Figure 1. Comparative analysis of UNCOVERseq and UNCOVER-DL to other nomination technologies.** Comparison of the sensitivity and precision of other published accounts of nomination technologies to nominate confirmable off-target sites using published EMX1 and FANCF gRNAs in HEK293-Cas9. Average method- specific sensitivity (nominated true positives / confirmed true positives) and precision (confirmed true positives /nominated true + false positives) was calculated for each method across both gRNAs (n = 2).

Request a consultation, scan the QR code or visit **idtdna.com/OTservices**

| FDA Expectation Area | How IDT Nomination & Confirmation Address It |
|---|---|
| On-target editing context | • Confirmation quantifies **on-and-off-target concurrently** using targeted deep sequencing via rhAmpSeq™ |
| Sequencing strategy & sensitivity | • Nomination uses **UNCOVERseq™ (cell-based, unbiased)** for sensitive genome-wide site discovery with described input requirements for benchmarked sensitivity<br>• Confirmation uses high-depth amplicon sequencing (>50,000x typically) to detect low-frequency edits using described input requirements with benchmarked performance |
| Off-target site nomination | • Primary method: **cell-based UNCOVERseq**, aligned with FDA preference for empirical nomination and appropriate quality controls determining performance bounds |
| Use of complimentary methods | • Nomination can be supplemented with ***in silico* predictions** (IDT-generated or client-supplied) to satisfy the FDA's expectation for orthogonal approaches |
| Sample selection – Biological relevance | • Nomination can be executed in customer-supplied cells (primary cells or cell lines) or IDT's promiscuous model cell line, justified and well-published as a sensitive proxy that **captures clinically relevant sites** |
| Reproducibility & replicates | • Nomination is performed in biological replicates by default, with demonstrated high reproducibility (~99% shared UMI reads) |
| Off-target confirmation | • Quantifies indels at **each nominated site** with defined analytical performance |
| Low-frequency event detection | • High-depth sequencing and statistical analysis are used to **distinguish true low-level edits from the background noise** |
| Chromosomal integrity / Rearrangements | • Confirmation workflow includes **assessment of genomic rearrangements/translocations** at nominated sites |
| Human genetic variation context | • Nomination reports include biological annotations (gene context, ClinVar, pathogenicity) to **help prioritize risk**<br>• Variant-aware analysis can be layered via *in silico* supplementation incorporating variants from HGDP and gnomAD |
| Reporting and transparency | • Nomination report includes: Reproducibility metrics, QC, ranked site lists, gene annotations and raw data<br>• Confirmation report includes: Site-level edit frequencies, gene annotations, risk-relevant context |
| IND-Enabling positioning | • Services are explicitly positioned for **IND-enabling safety assessment or reviewer-ready publication** |

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*Data provided is intended to identify potential off-target risks associated with customer-defined gRNAs and may be used alongside other studies to support risk characterization under FDA April 2026 draft guidance on human genome editing. It is for informational purposes only and should not be the sole basis for decision-making.*

IDT™ INTEGRATED DNA TECHNOLOGIES