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Genomic Safety Assessment with ecNGS: The Next Generation

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Error-corrected next-generation sequencing (ecNGS) is an effective tool for not only detecting the induction of mutations from a carcinogenic exposure, but in carefully quantifying individual mutations too. The current genetic toxicology test battery includes several in vitro and in vivo mutation assays but their applicability to different genomic loci, tissues, organs, and species is limited. ecNGS methods promise disruption to the field of genomic safety with richer data, broader applicability, greater accessibility, and universal translation given that the analyte of the assay is simply DNA.

NGS technologies, in general, output nucleotide resolution data at incredible speed and throughput which, when coupled with the increase in accuracy from an error-corrected approach, enable ultra-sensitive mutation detection. At this scale, rare mutational data can be used for advanced bioinformatics analysis such as mutation spectra deconvolution, pattern matching, and inferring the mode of action of a mutagenic exposure.

Among ecNGS techniques exists duplex sequencing which improves sequencing accuracy over standard NGS by 100,000-fold and permits the detection of rare de novo mutations at frequencies of 1×10-8 through a process of independently tracking both strands of individual DNA molecules and then comparing the strands to eliminate technical errors.

Recent advances in using ecNGS for genomic safety assessment have proved innovative, and multiple ecNGS approaches now exist for generating a mutagenesis or carcinogenesis readout. This talk will summarize the history of ecNGS as a tool for genomic safety, the current landscape of ecNGS options for mutagenesis and carcinogenesis readouts, and reveal how ecNGS should transform the future of not only drug and chemical safety assessment but also of optimizing gene editing therapies, assessing the life-integrated mutagenic exposures of living individuals, linking contamination to cancer clusters, and biomonitoring those at risk to occupational carcinogens such as firefighters and astronauts.

Keywords:
ecNGS; mutagenesis; genetic toxicology; genomics; duplex sequencing.