

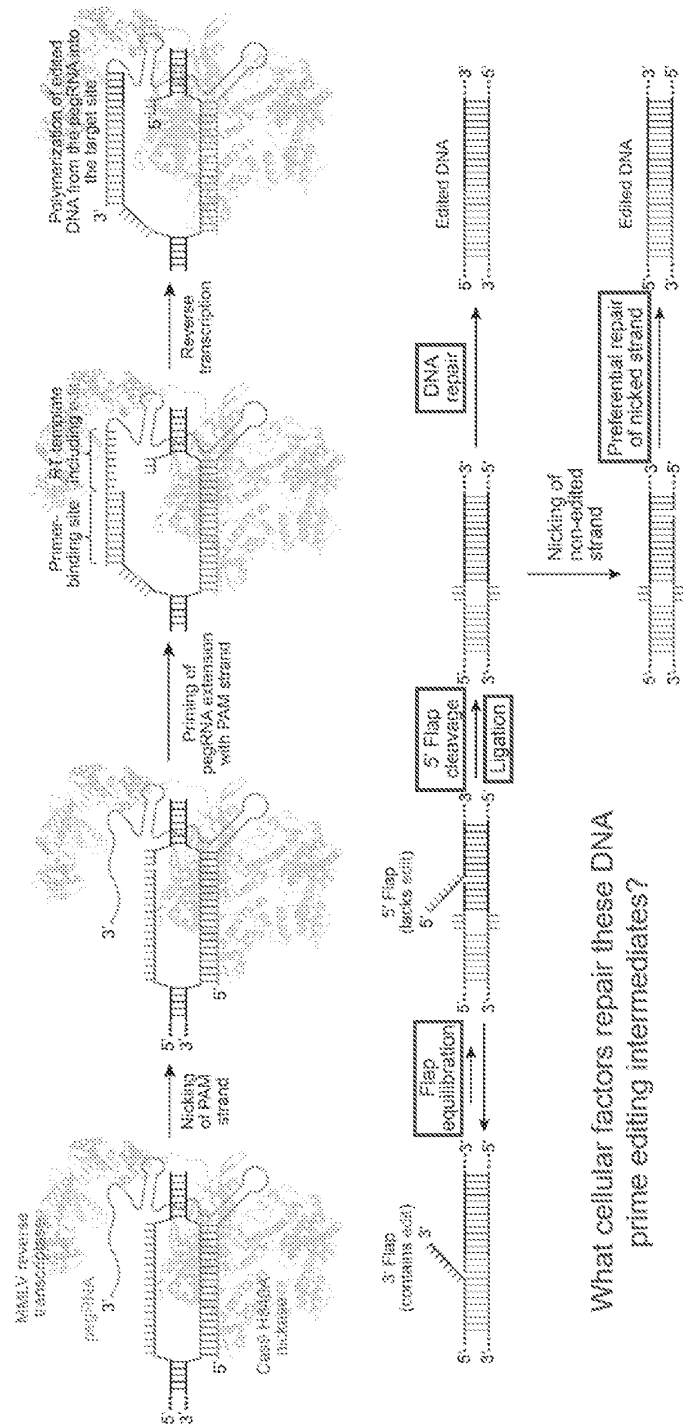


FIG. 1

What cellular factors repair these DNA prime editing intermediates?

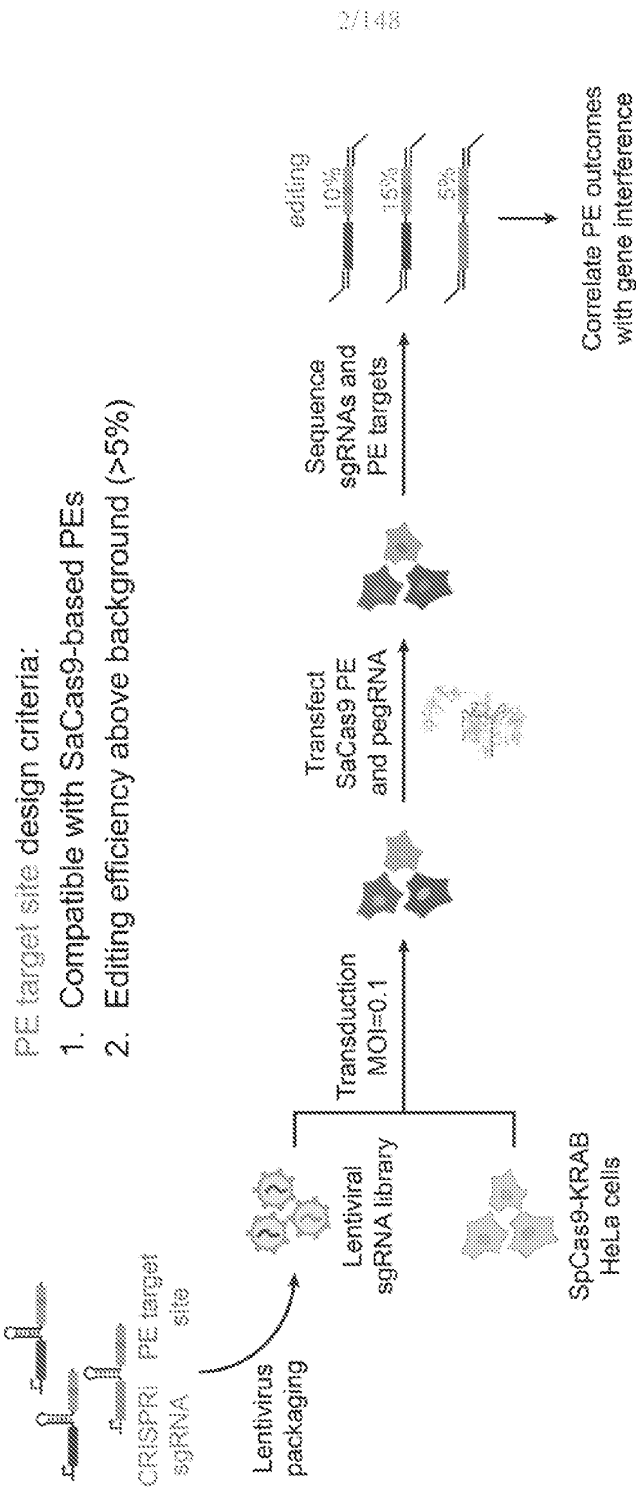


FIG. 2

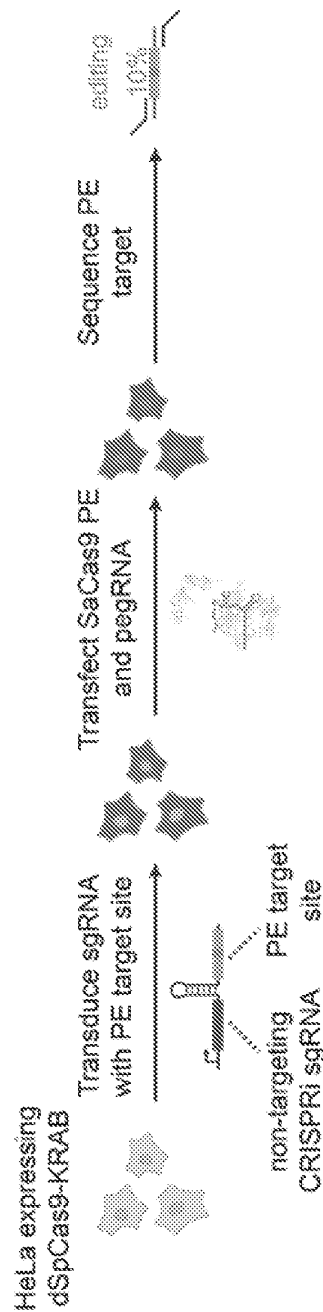


FIG. 3A

Target site editing, HeLa

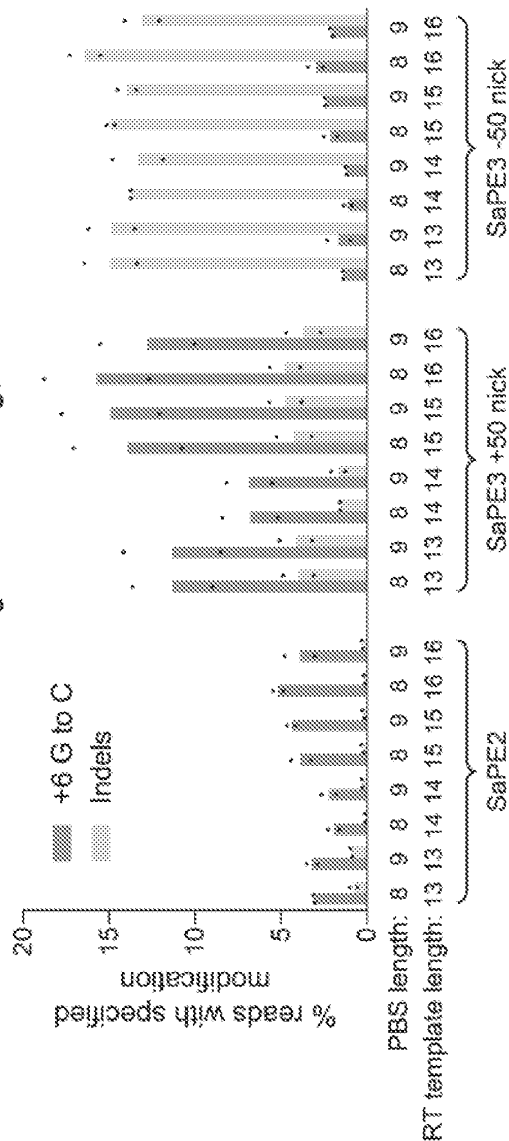


FIG. 3B

Target site editing with
blastocidin selection, HeLa

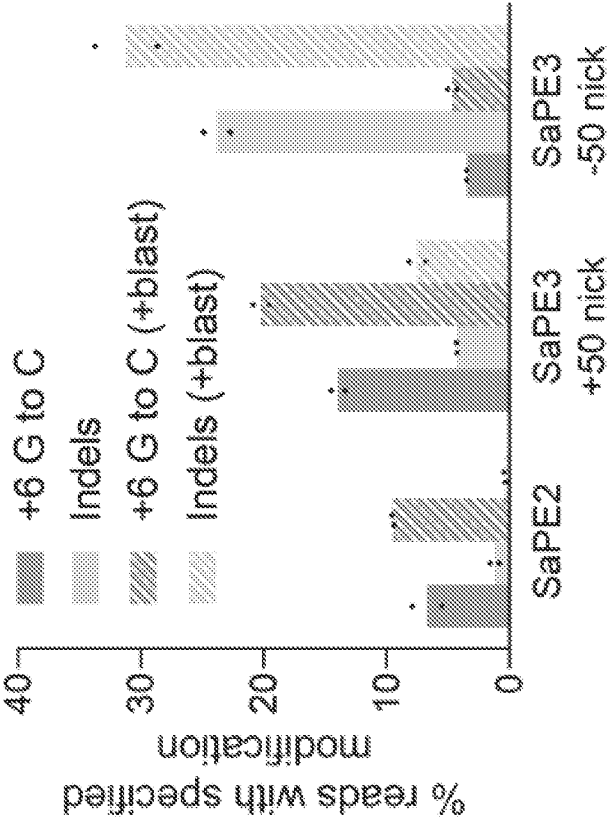


FIG. 3C

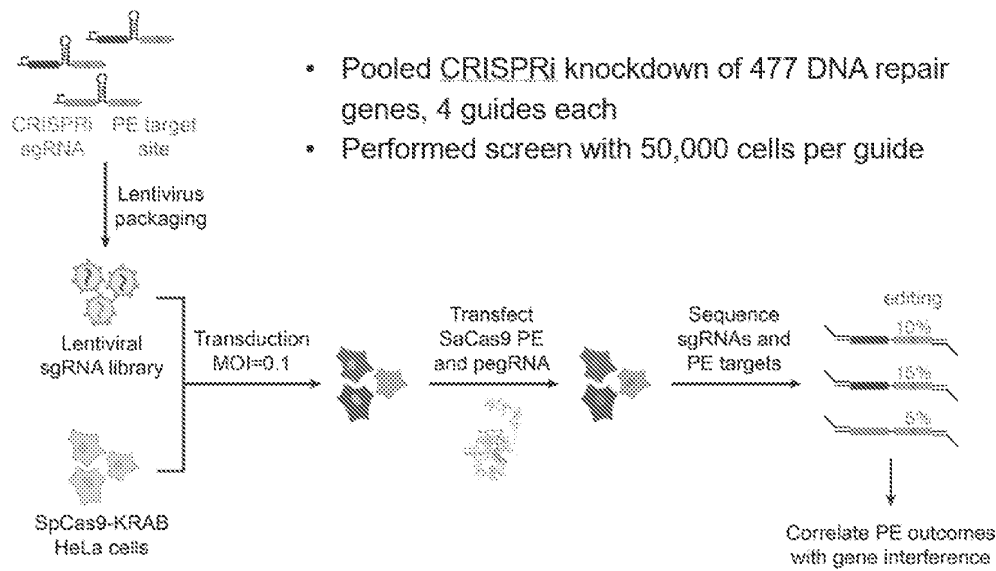


FIG. 4A

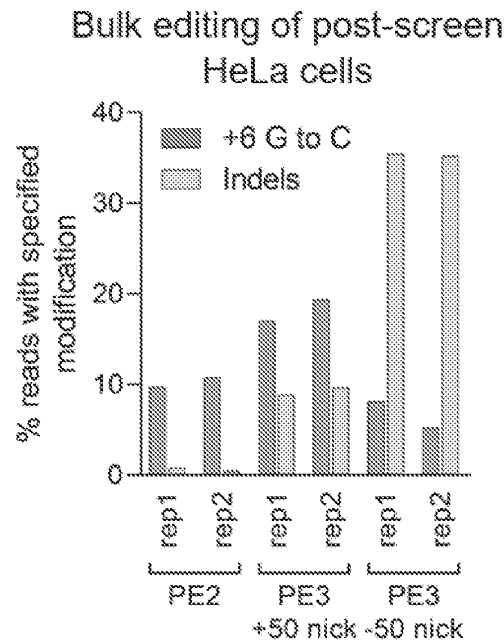


FIG. 4B

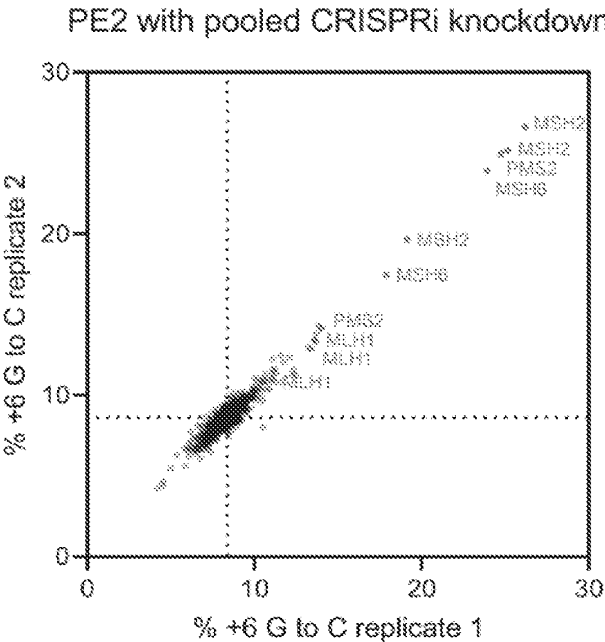


FIG. 5A

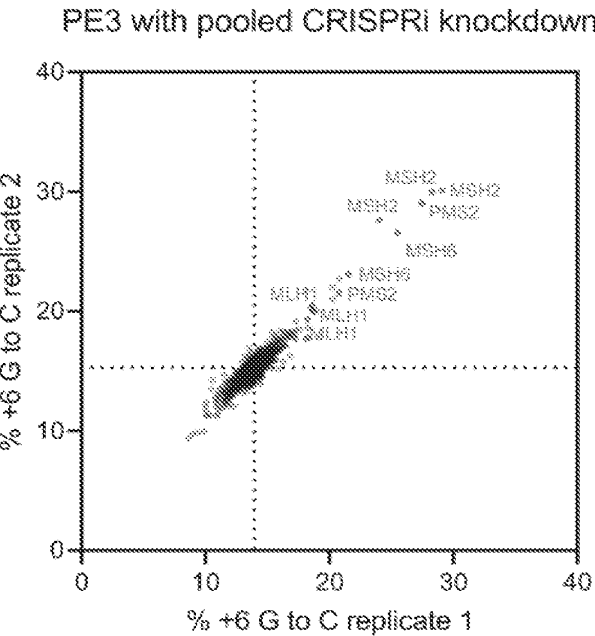


FIG. 5B

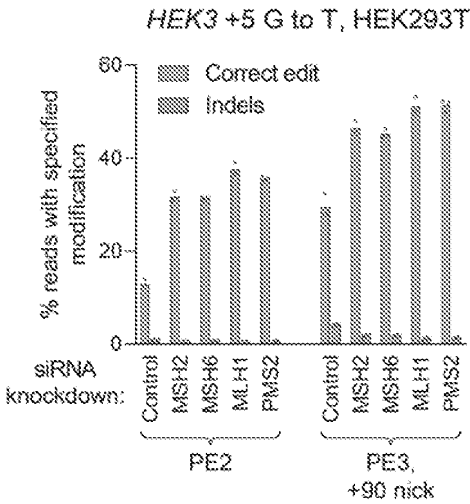


FIG. 6A

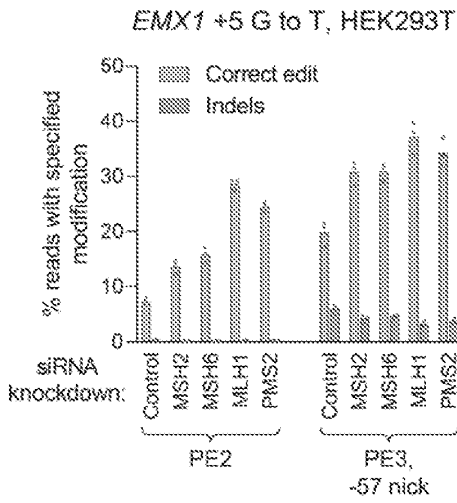


FIG. 6B

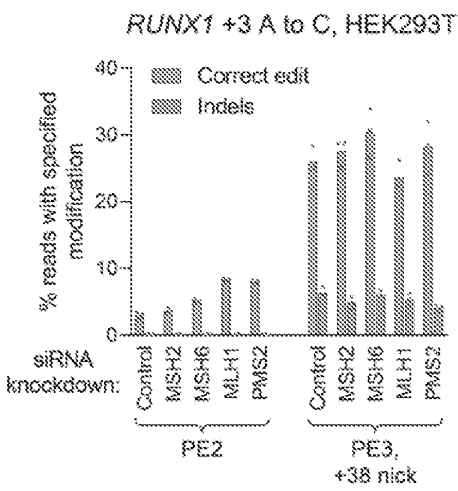


FIG. 6C

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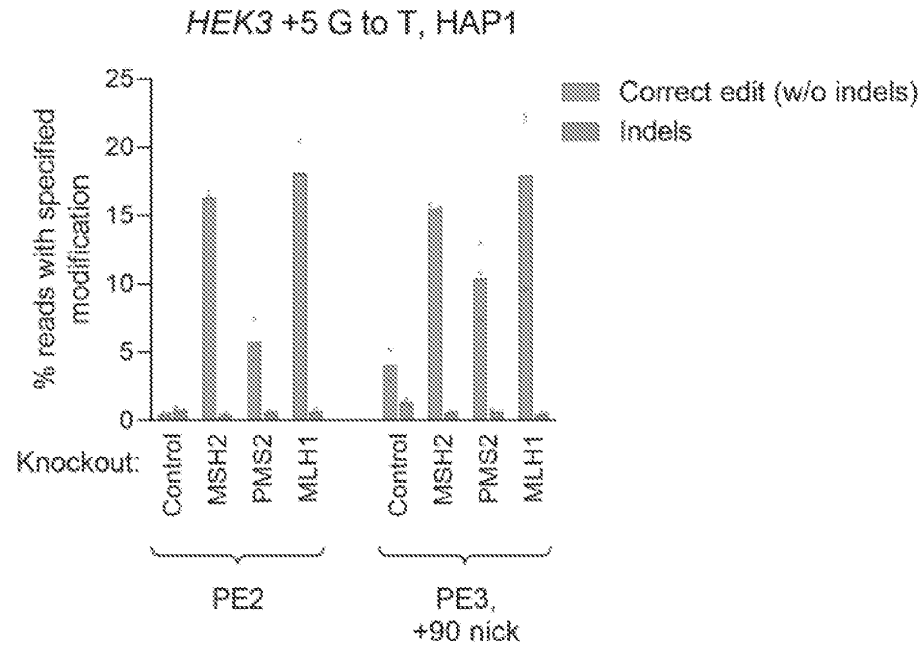


FIG. 7A

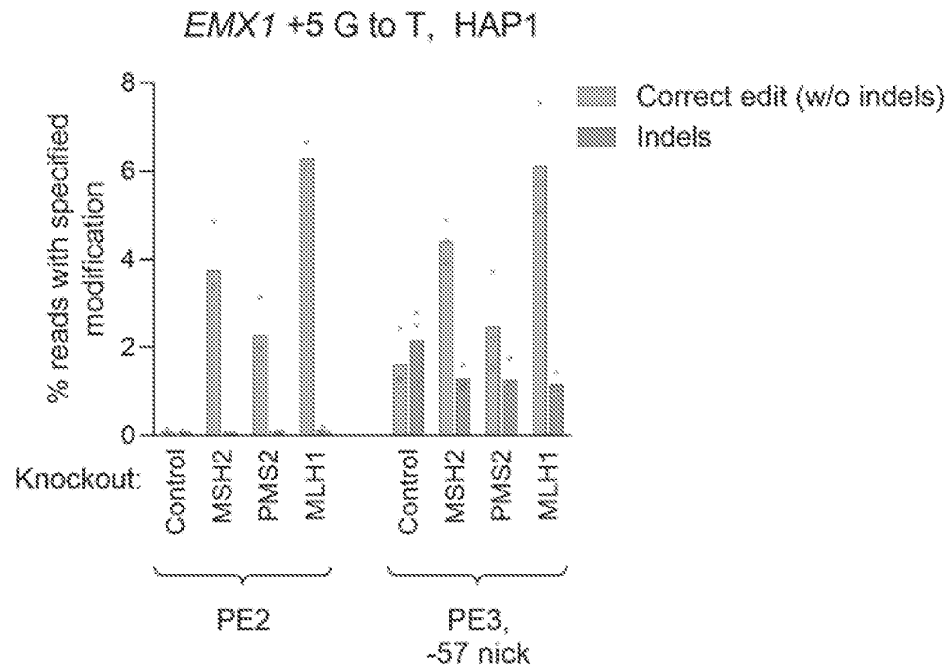


FIG. 7B

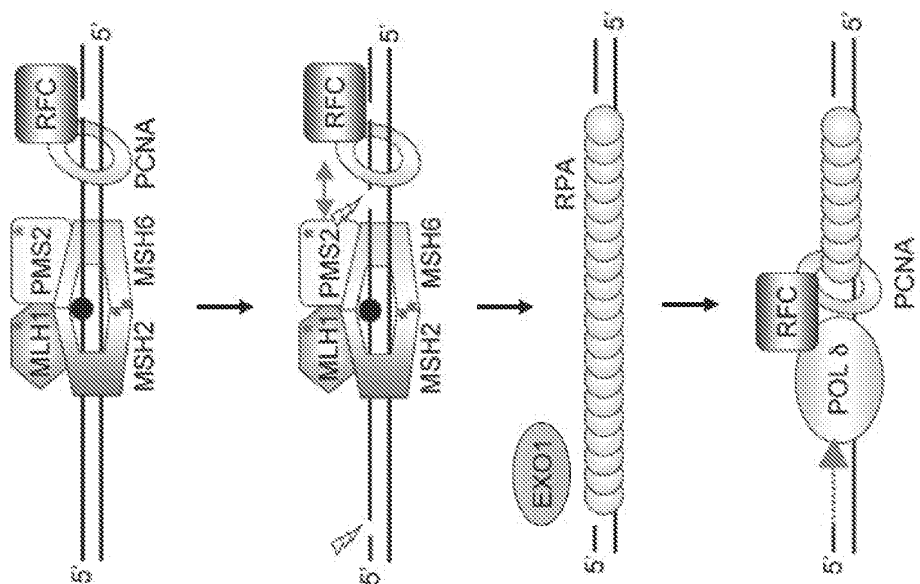


FIG. 8A

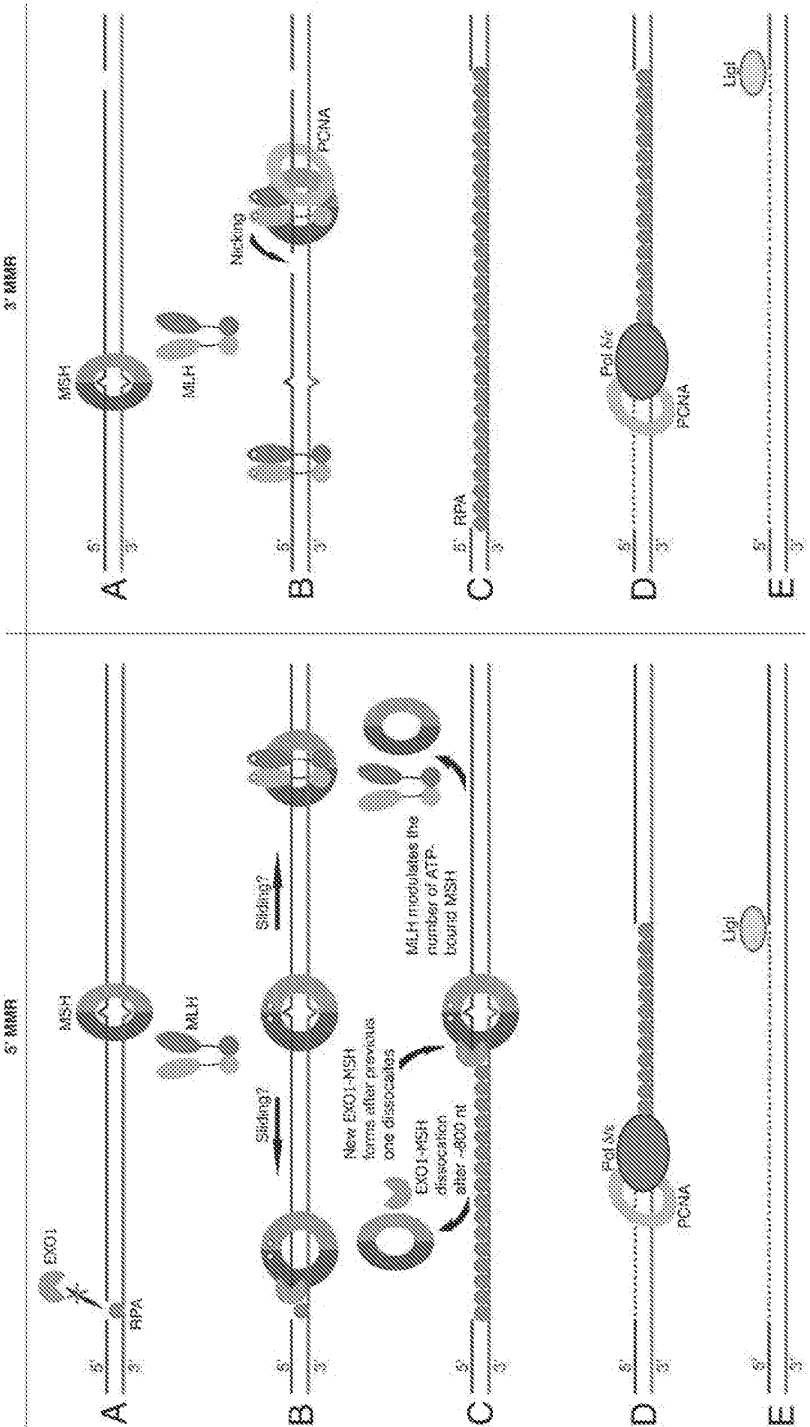


FIG. 8B

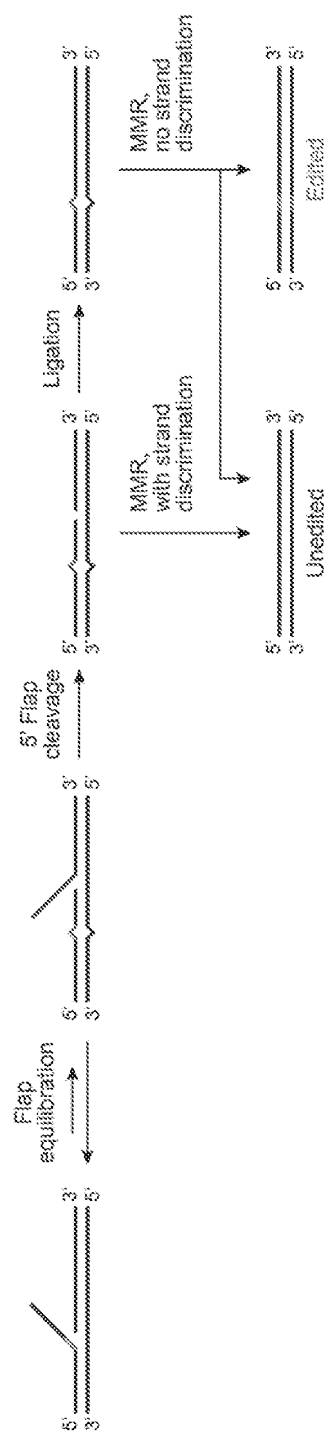


FIG. 9A

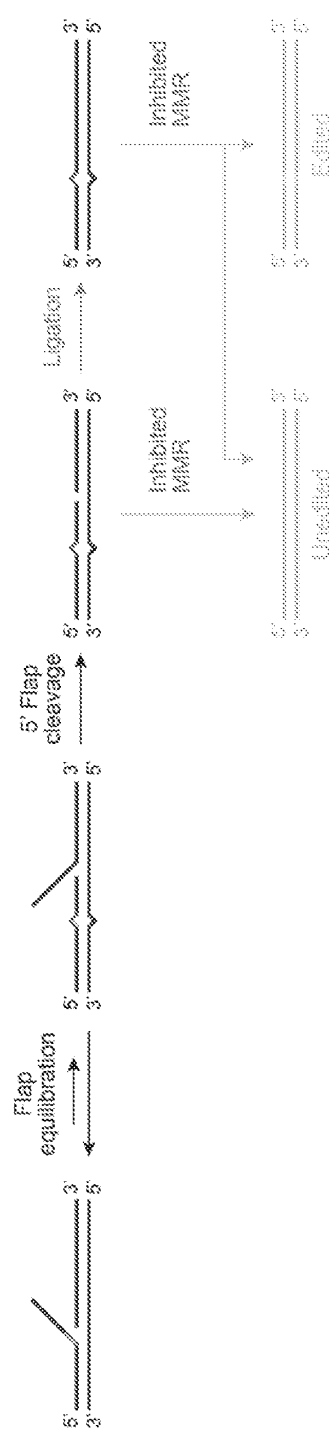


FIG. 9B

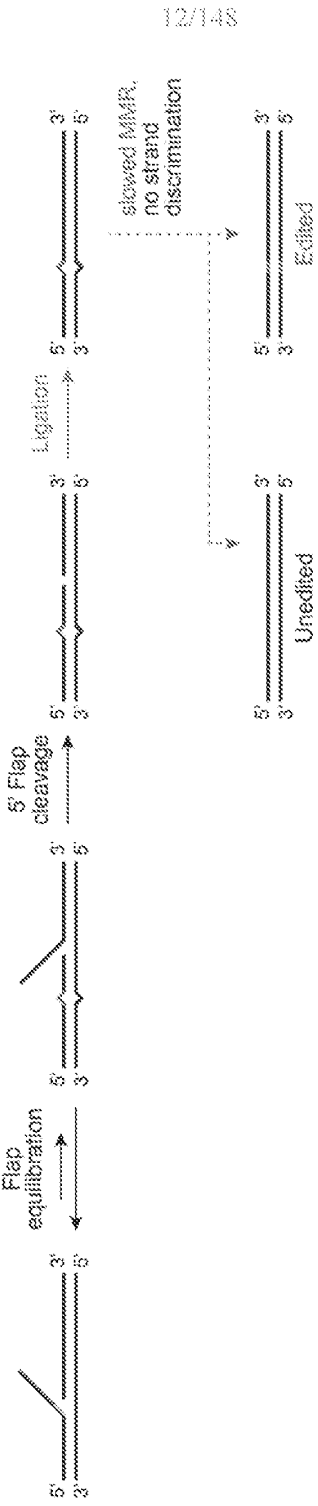


FIG. 9C

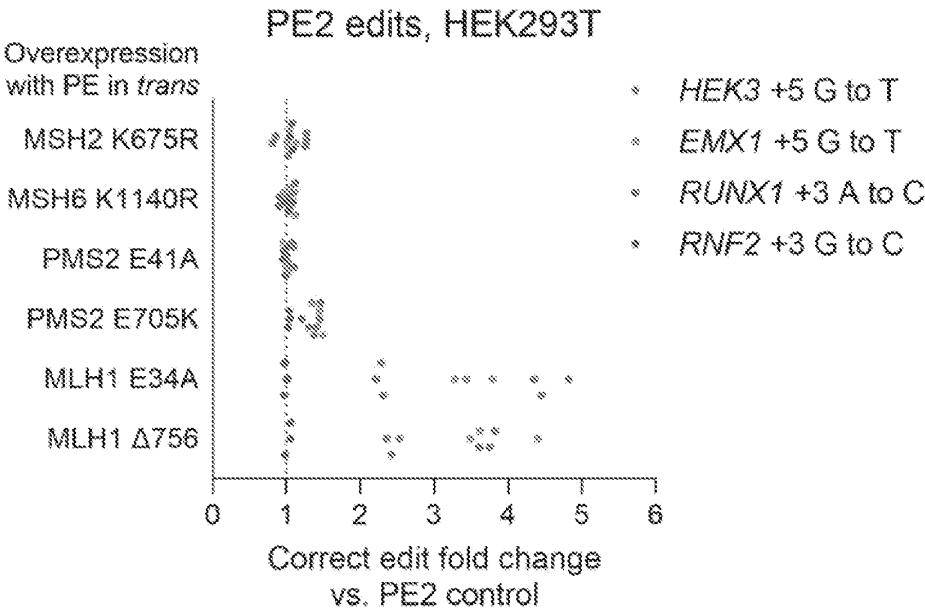


FIG. 10

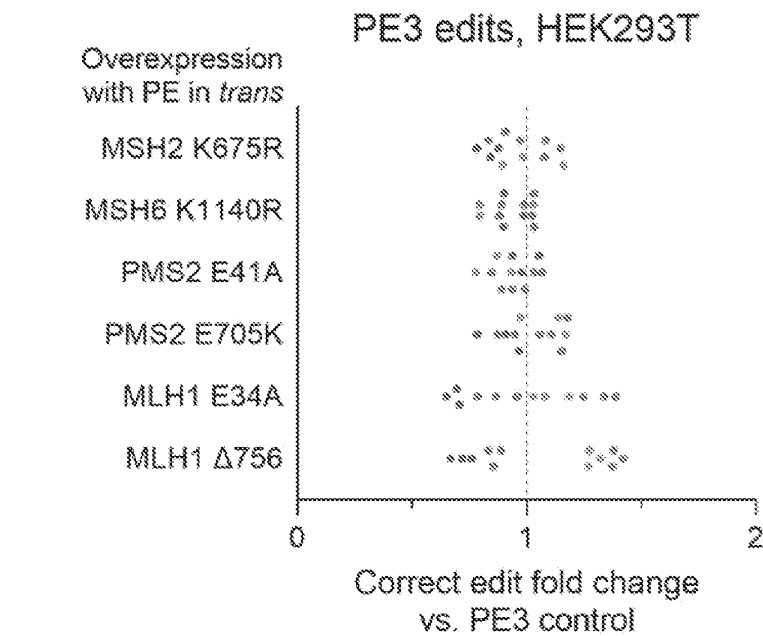


FIG. 11A

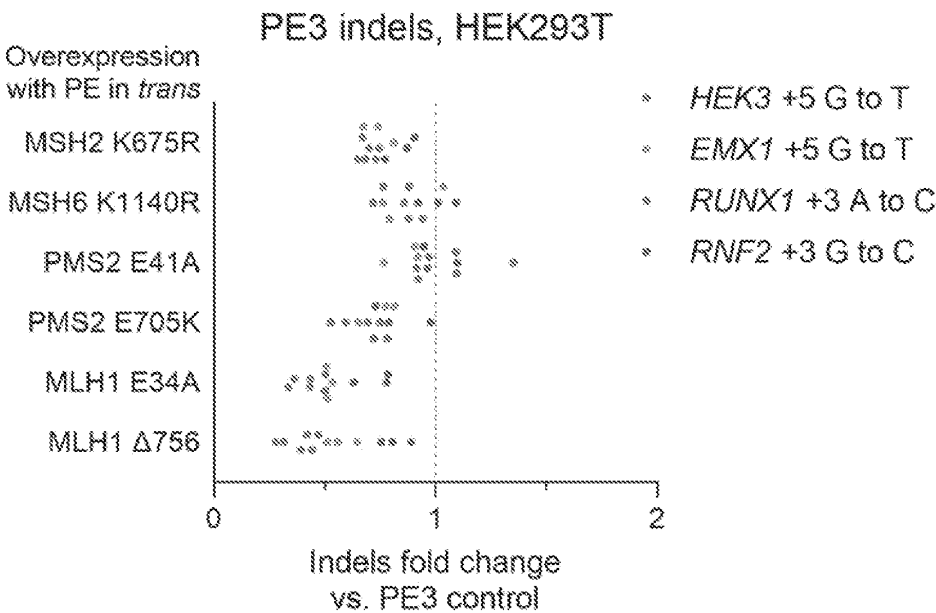


FIG. 11B

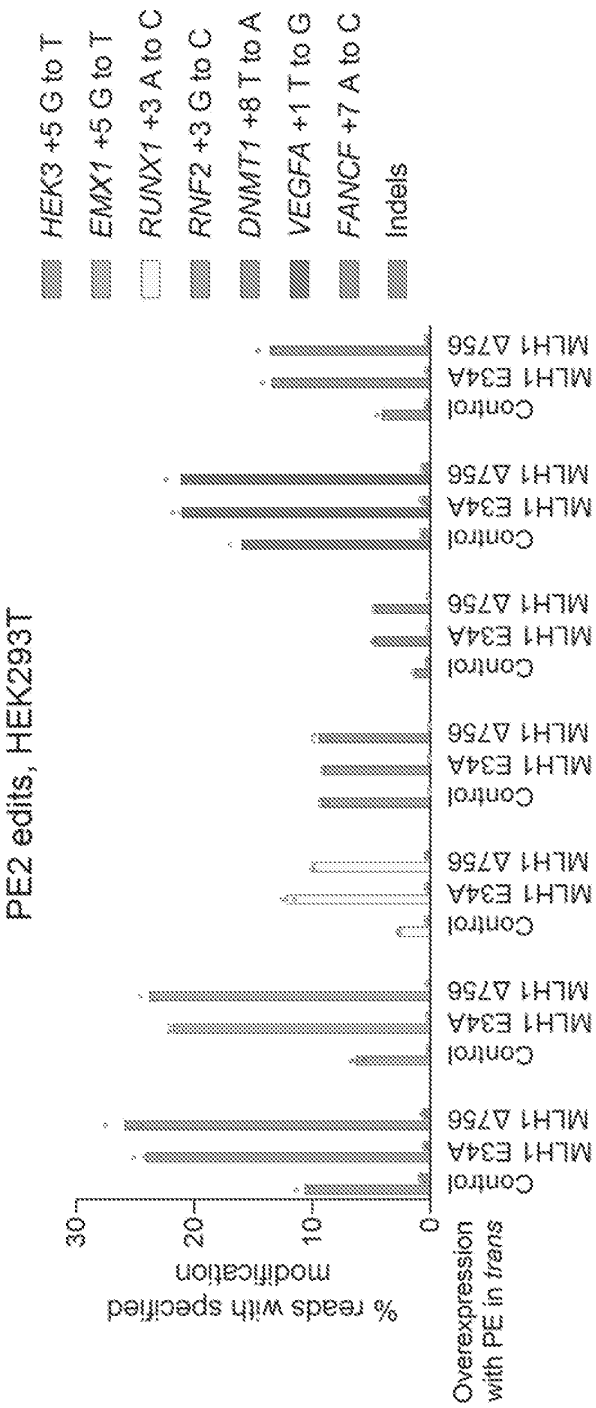


FIG. 12A

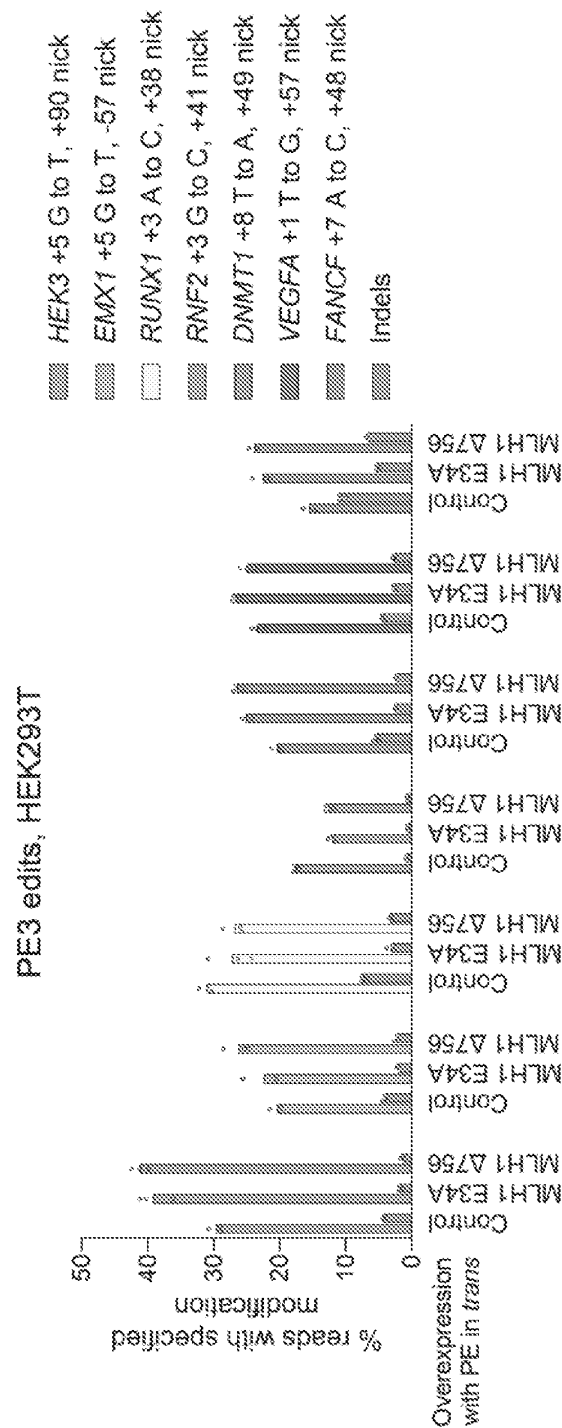


FIG. 12B

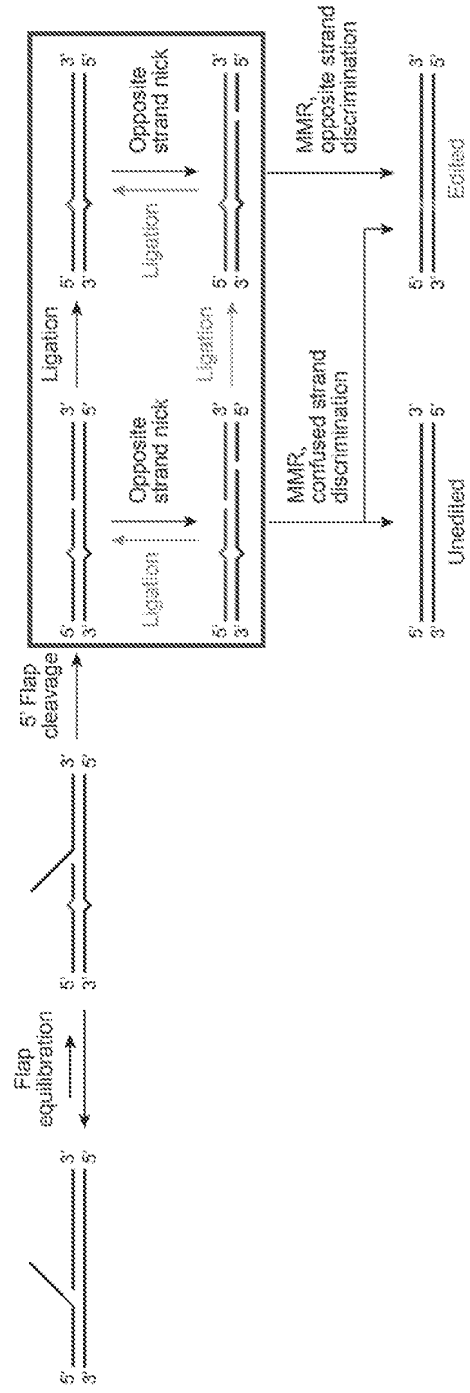


FIG. 13

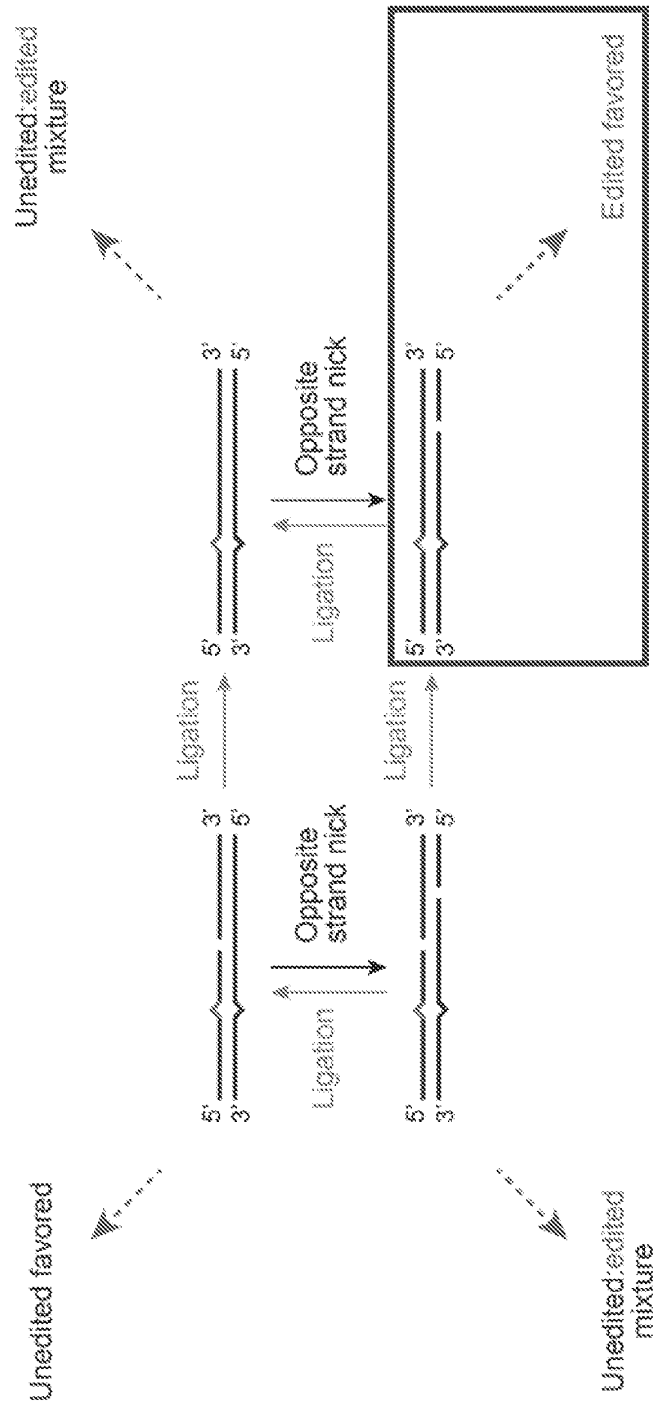


FIG. 14

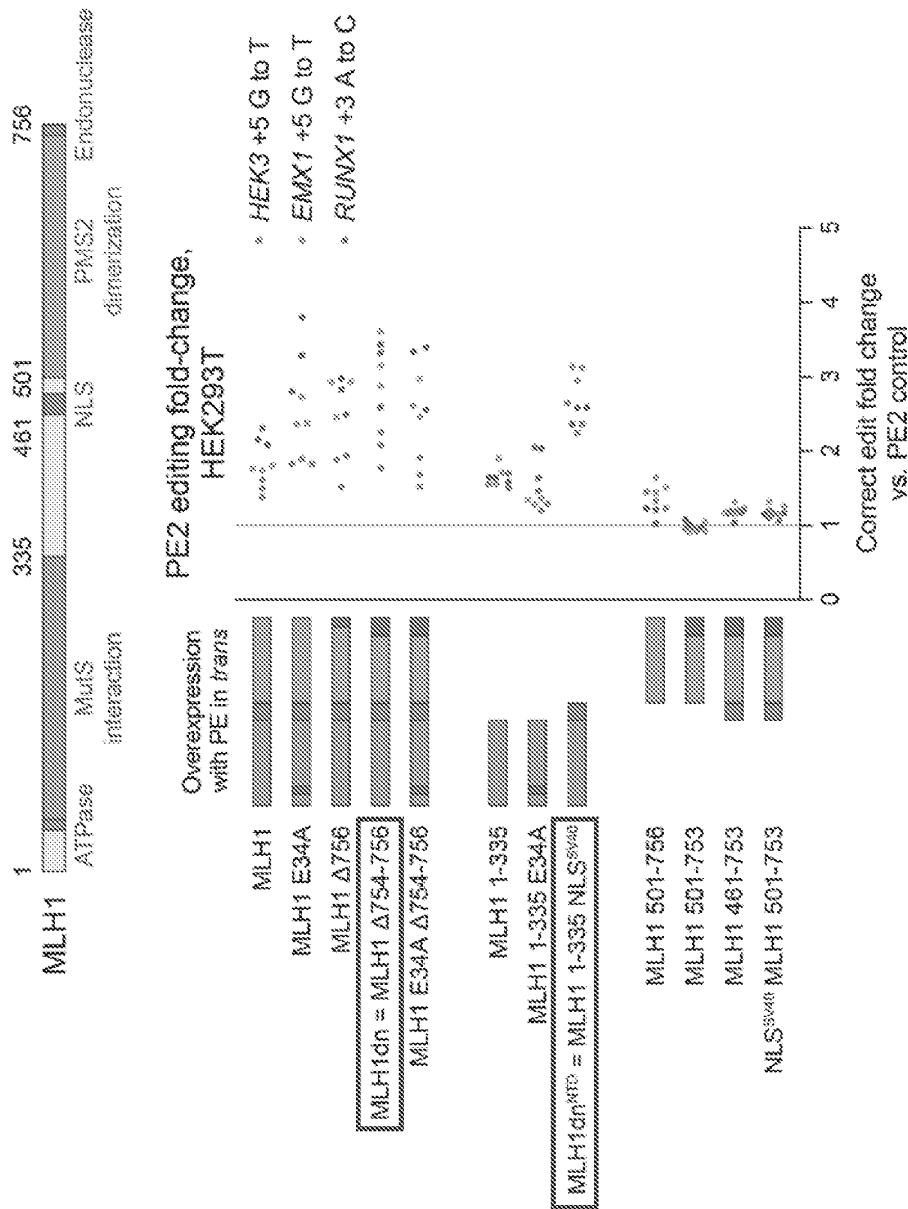


FIG. 15A

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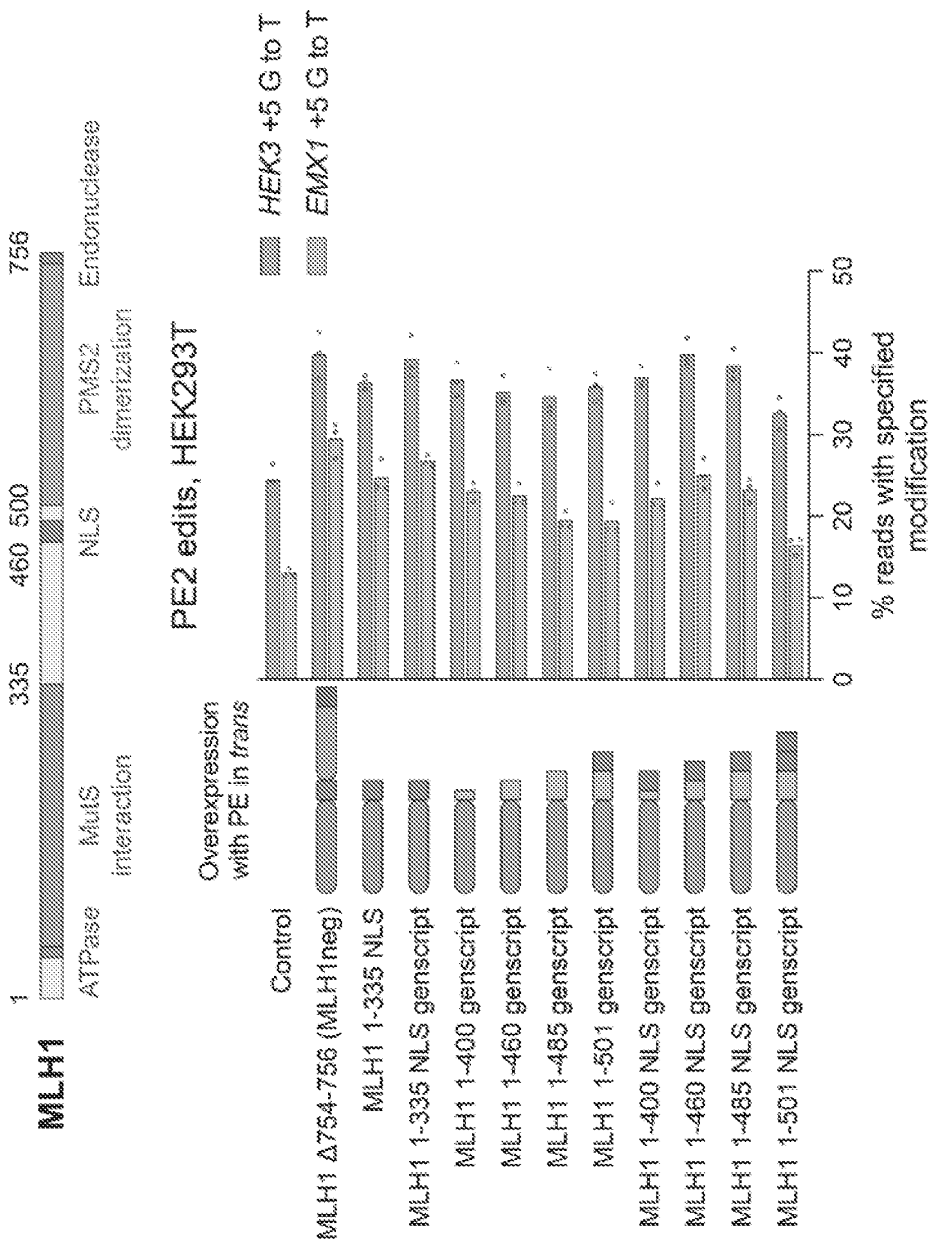


FIG. 15B

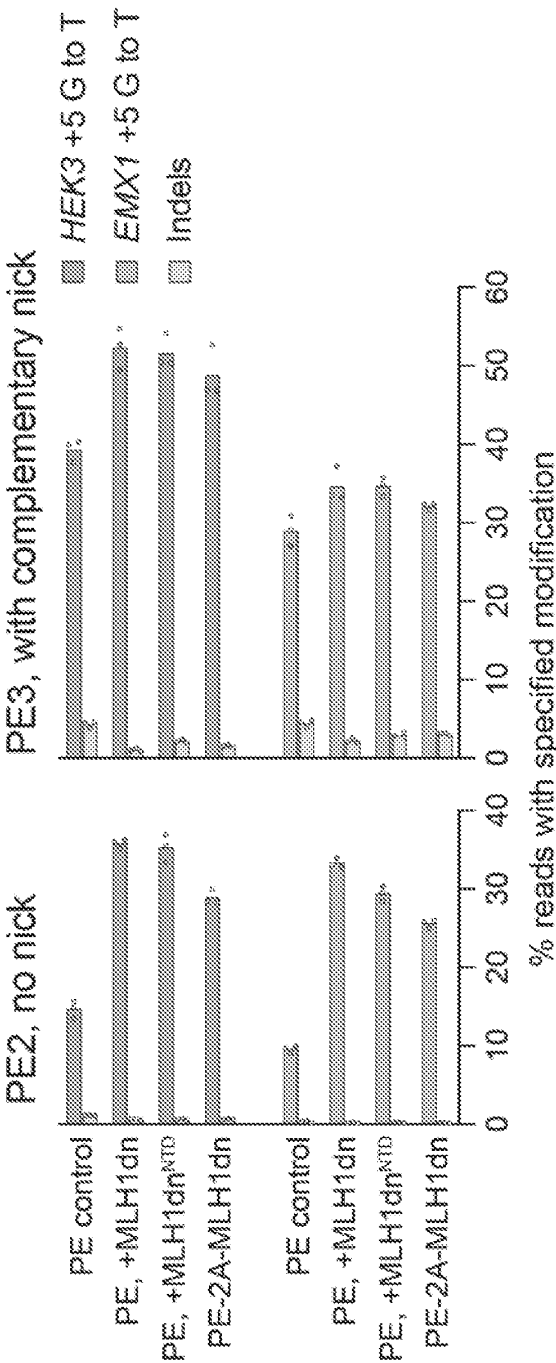


FIG. 15C

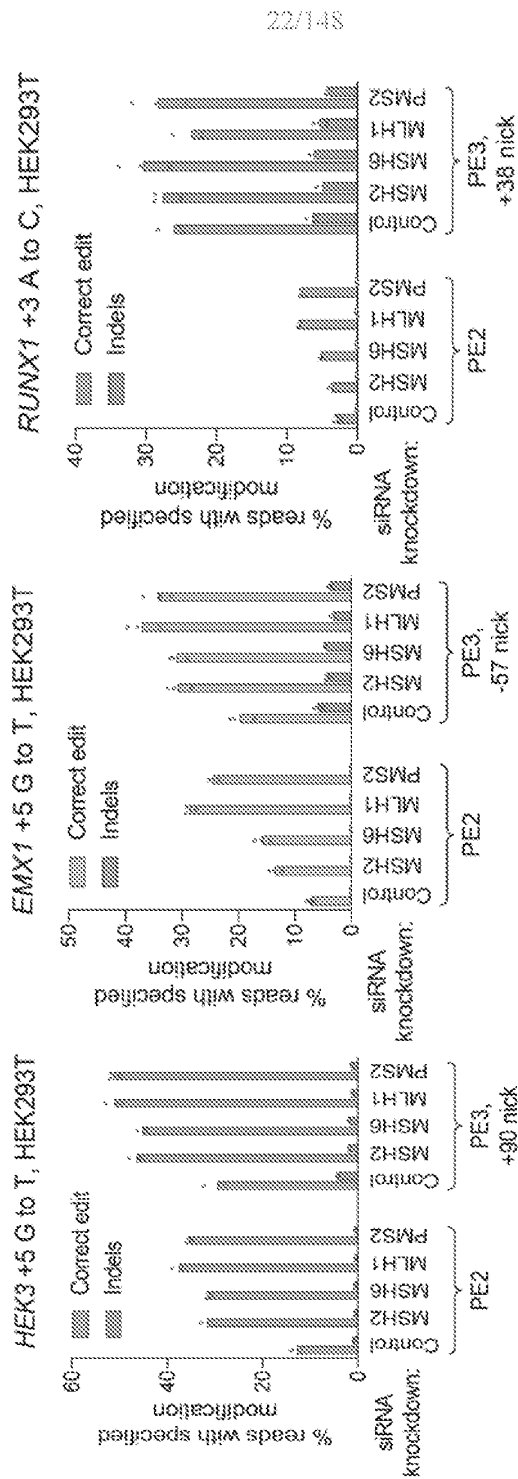


FIG. 15D

FIG. 15E

FIG. 15F

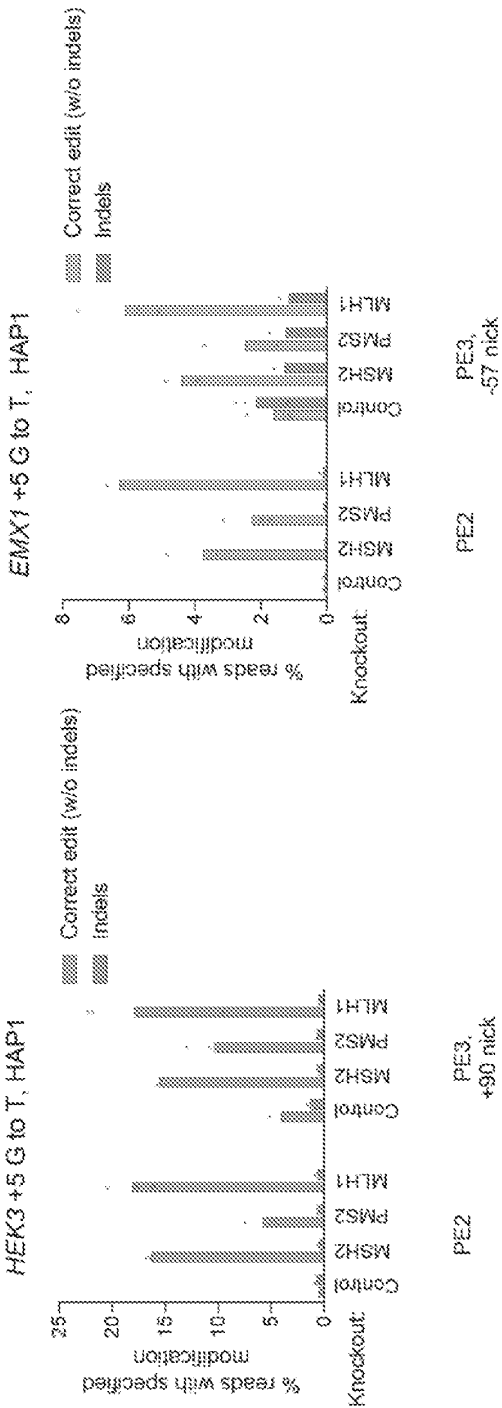


FIG. 15H

FIG. 15G

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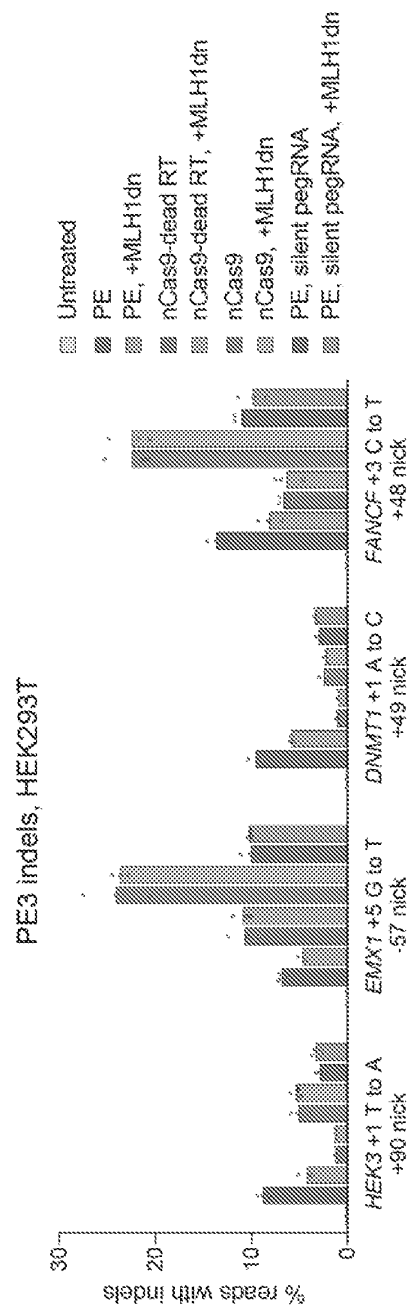


FIG. 16

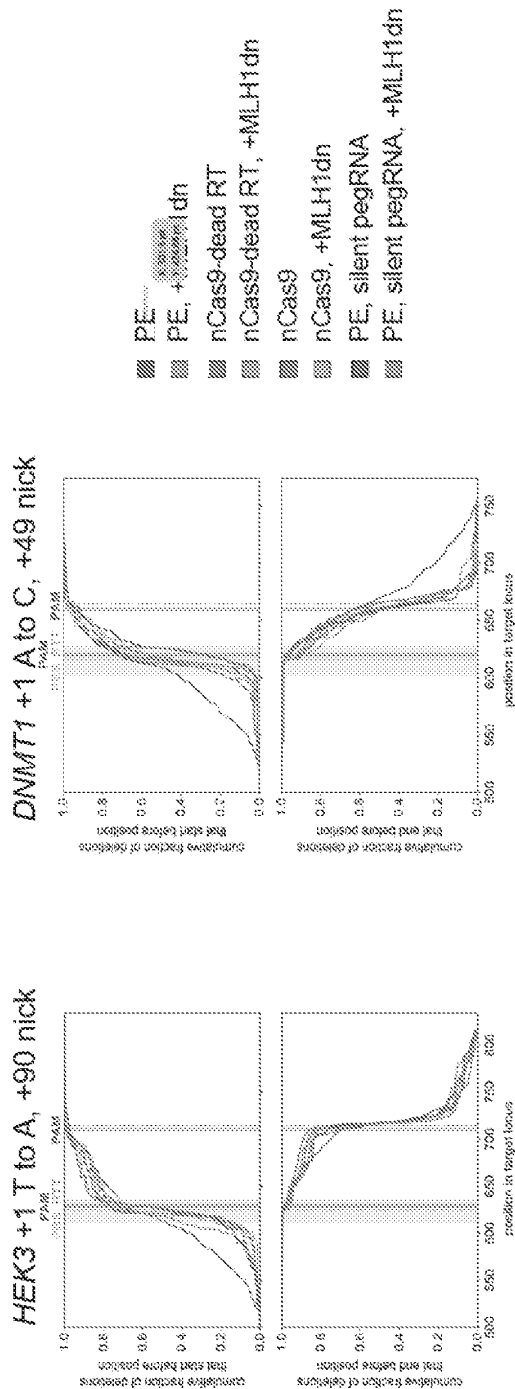


FIG. 17

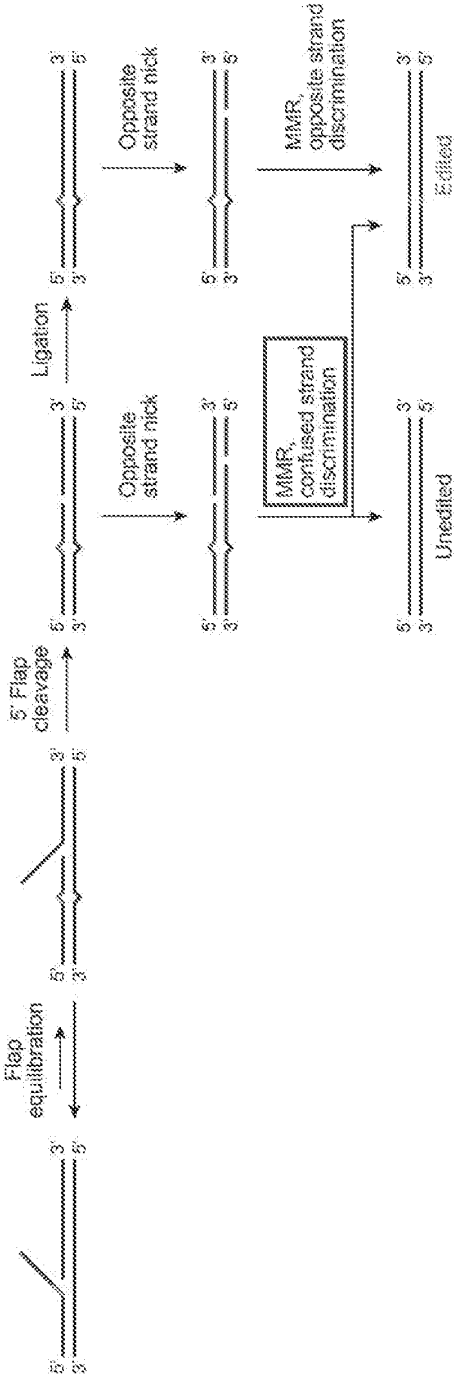


FIG. 18

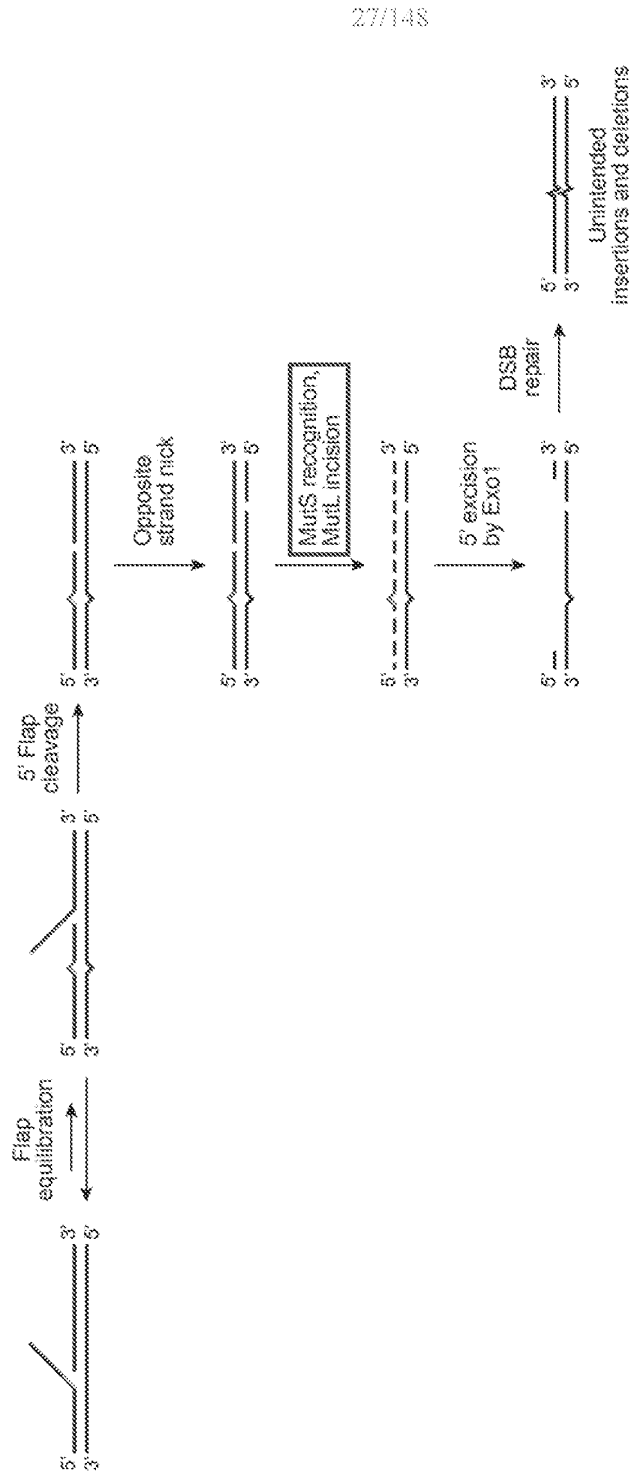


FIG. 19A

DNMT1 +1 A to C, +49 nick

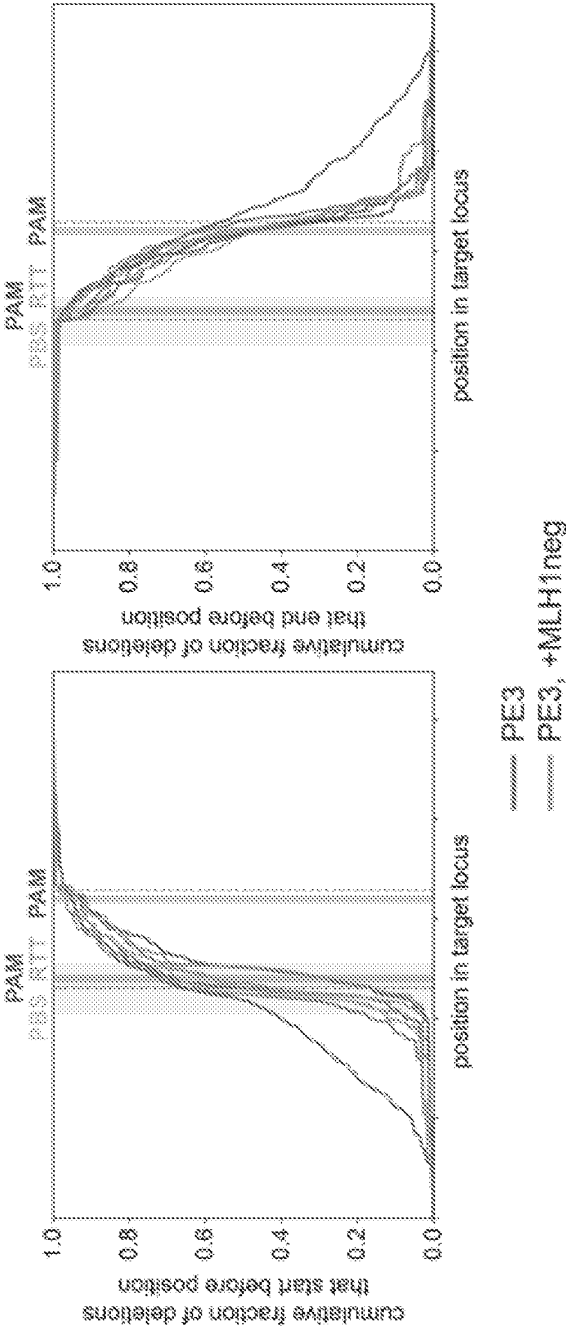


FIG. 19B

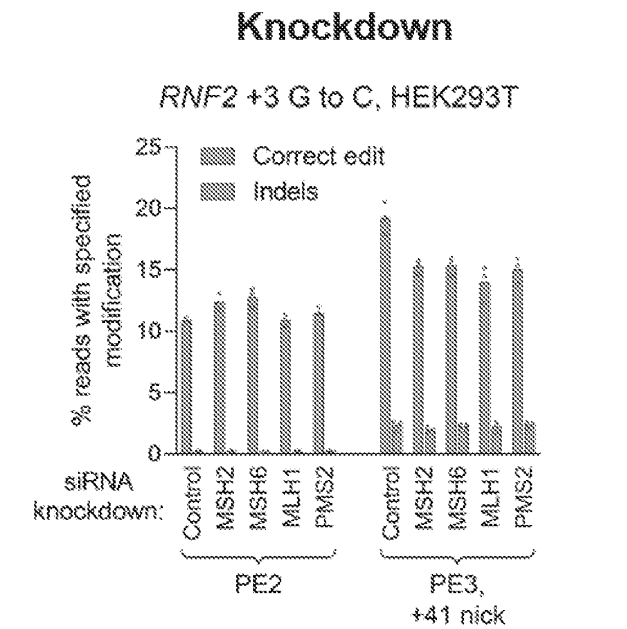


FIG. 20A

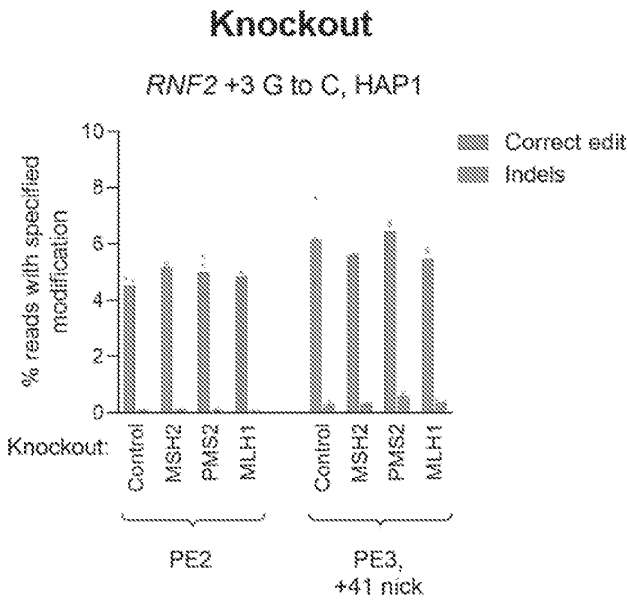


FIG. 20B

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PE2, *RNF2*, HEK293T

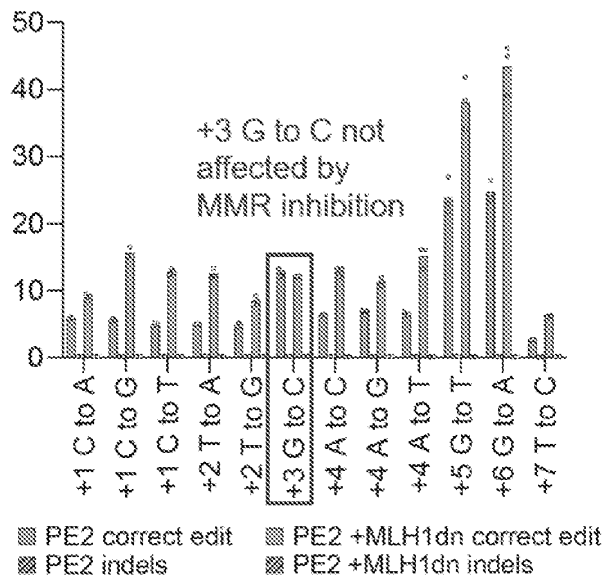


FIG. 21A

PE2 at *RNF2*, HEK293T

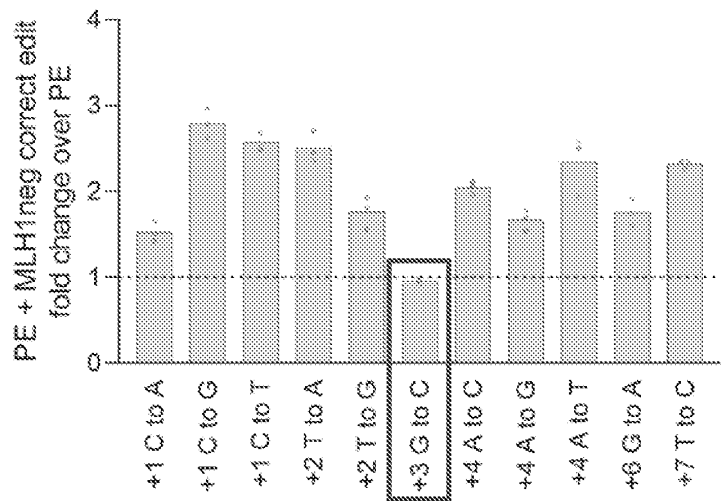


FIG. 21B

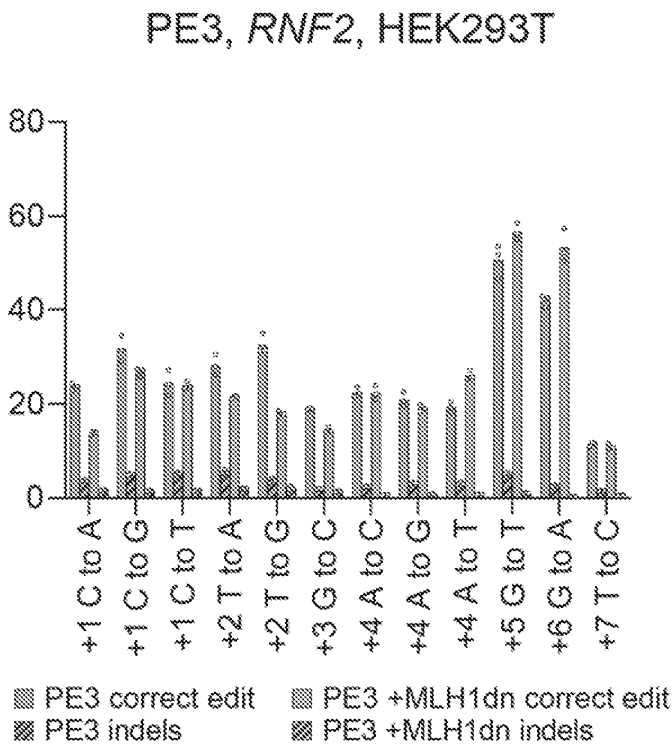


FIG. 21C

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PE2, *HEK3*, HEK293T

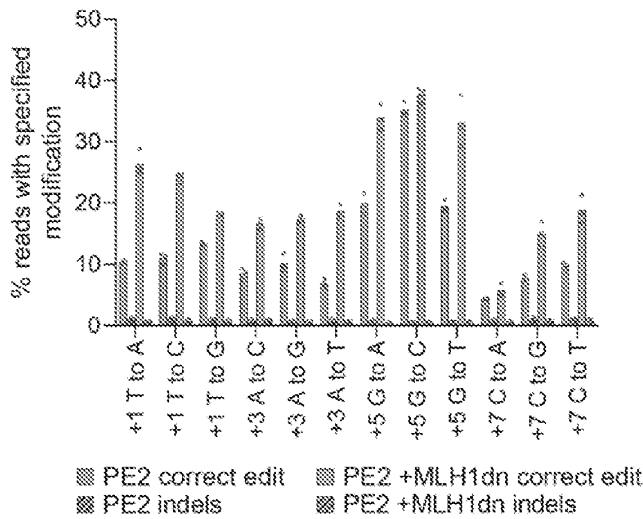


FIG. 22A

PE3, *HEK3*, HEK293T

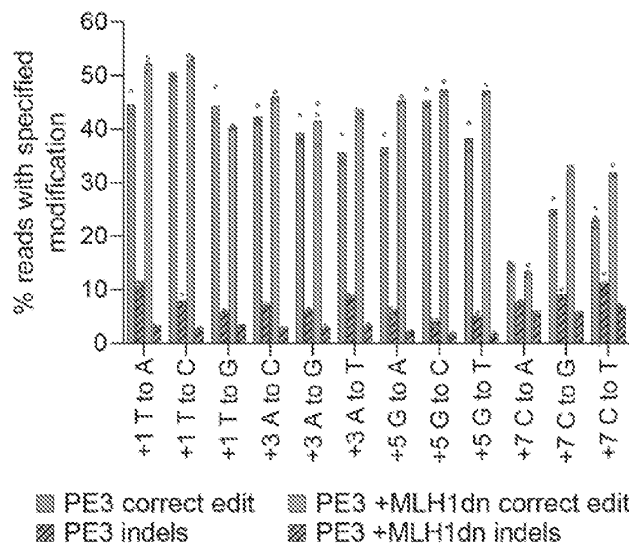


FIG. 22B

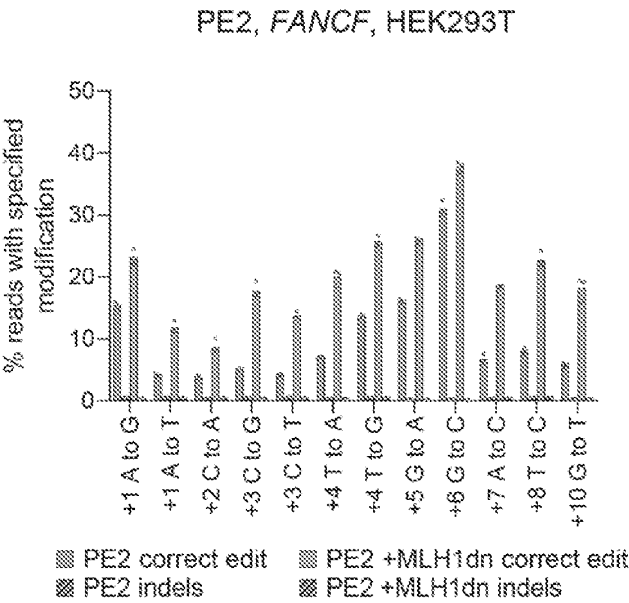


FIG. 23A

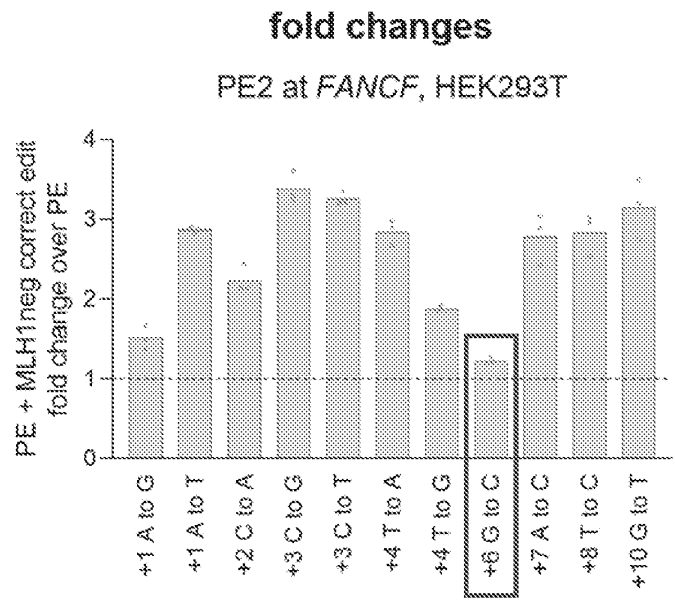


FIG. 23B

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PE3, *FANCF*, HEK293T

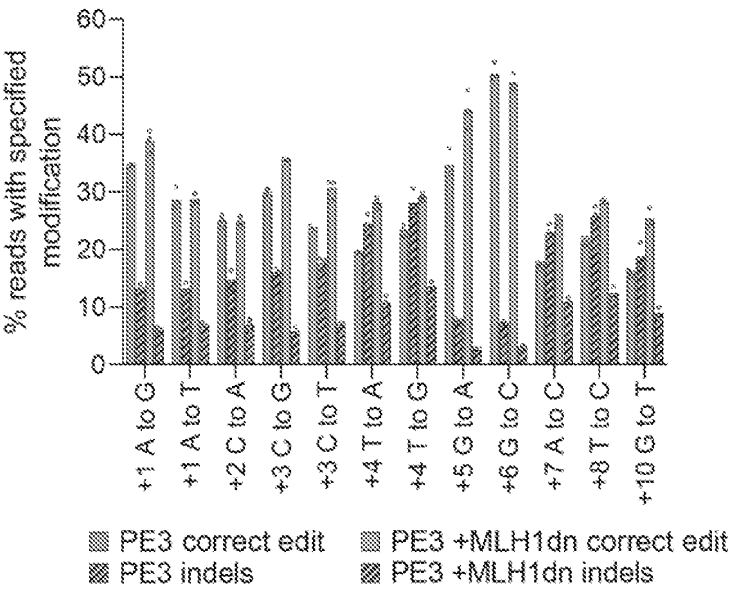


FIG. 23C
PE3 +48 nick at *FANCF*, HEK293T

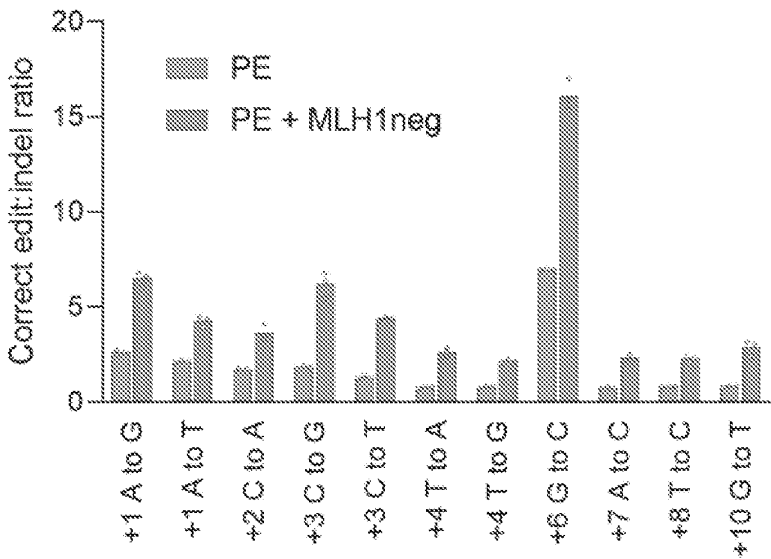


FIG. 23D

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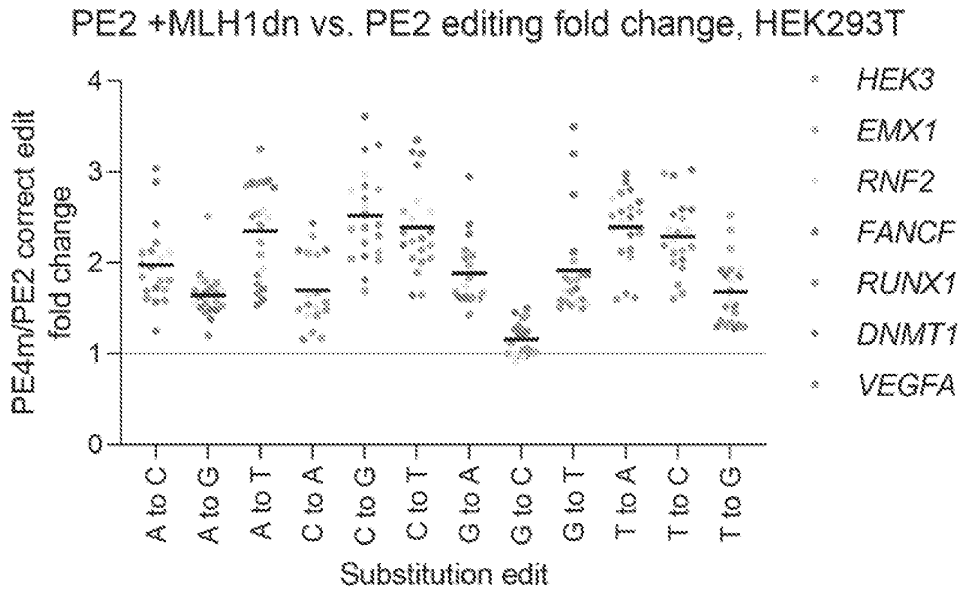


FIG. 24A

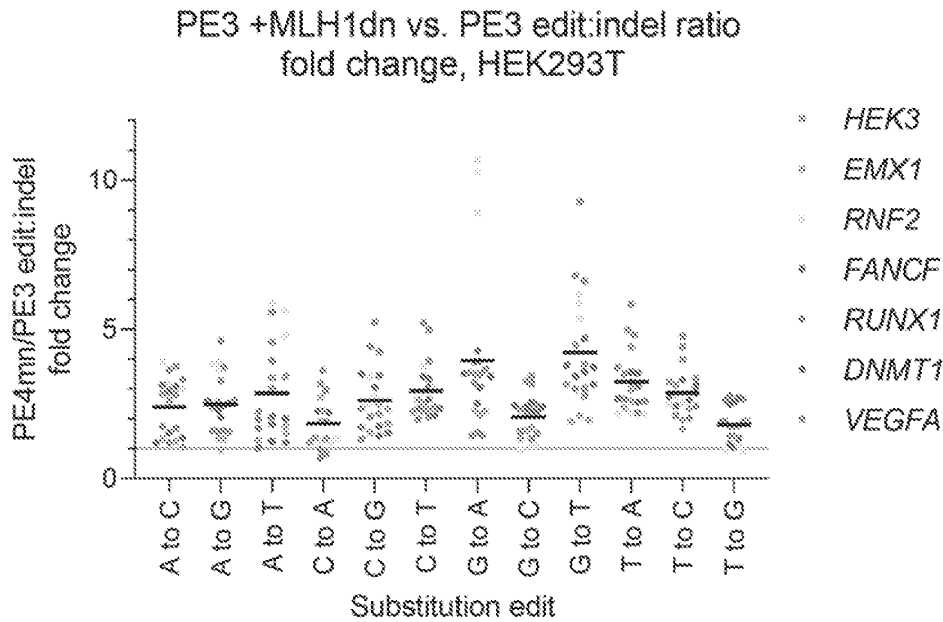


FIG. 24B

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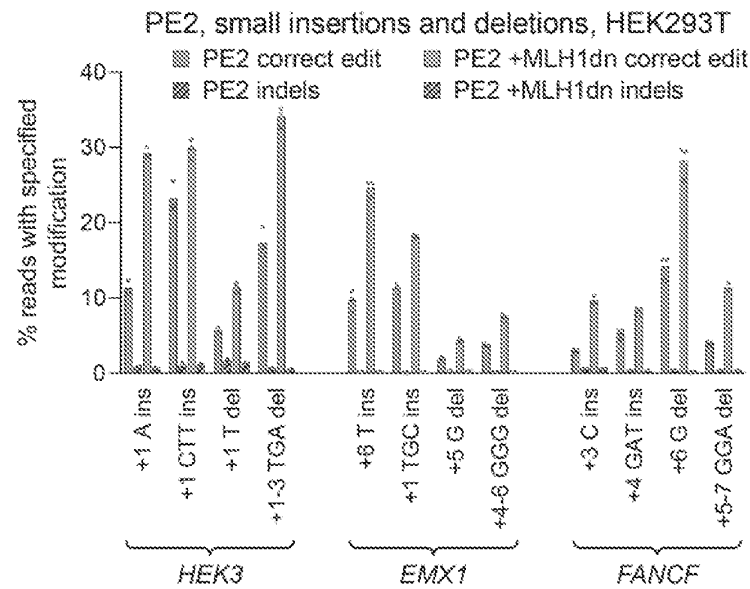


FIG. 25A

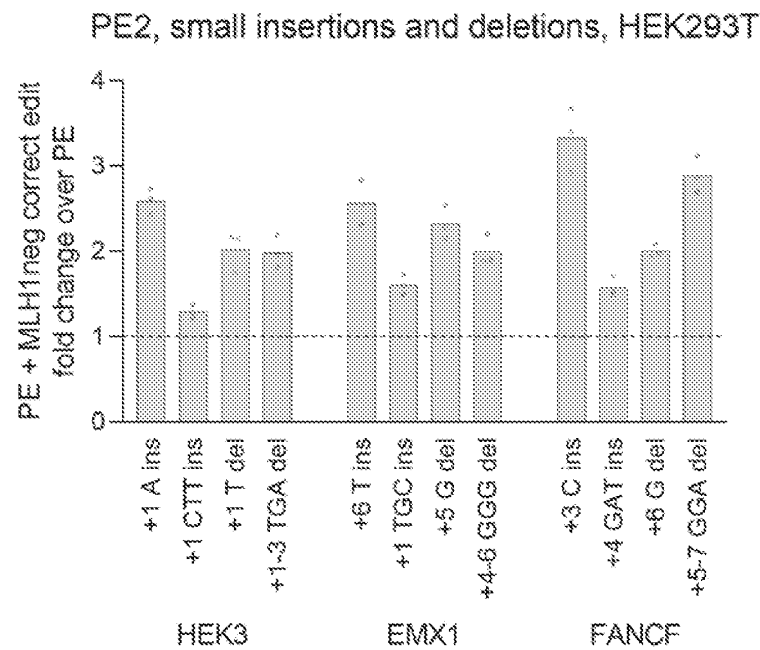


FIG. 25B

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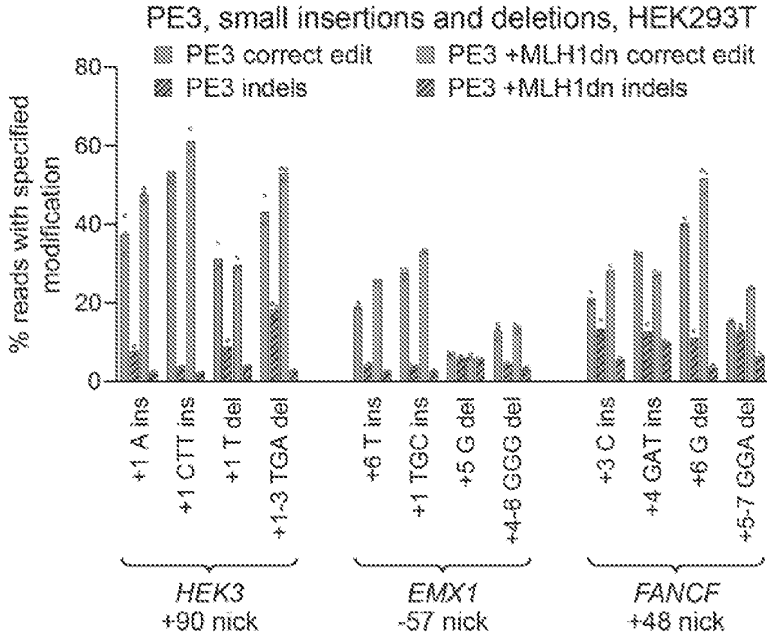


FIG. 25C

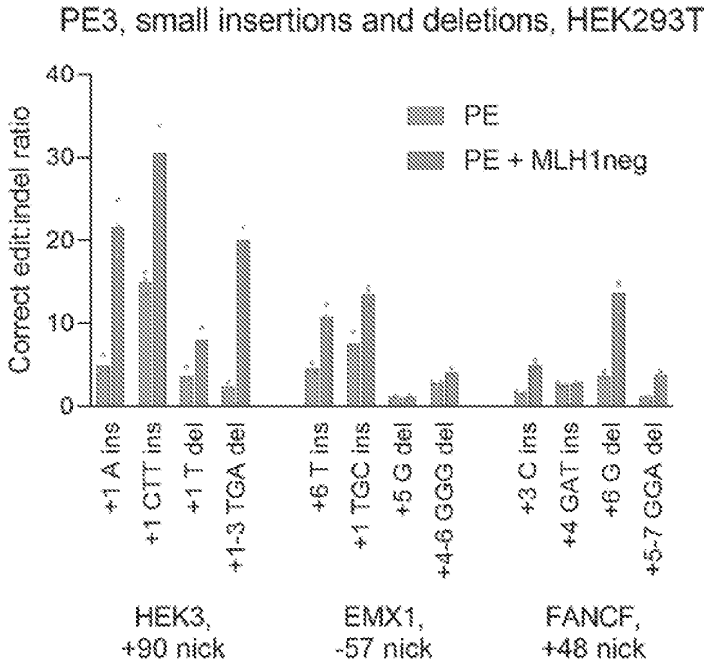


FIG. 25D

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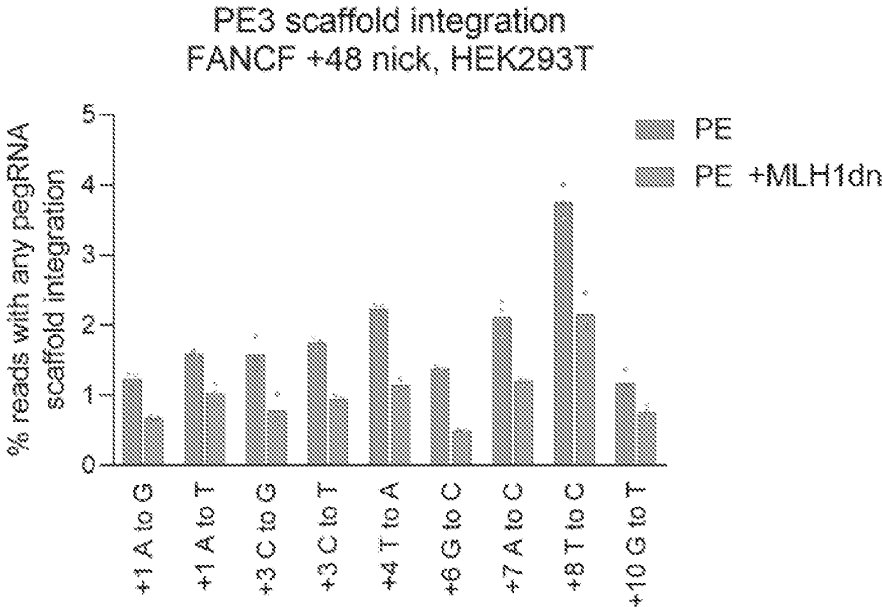


FIG. 26A

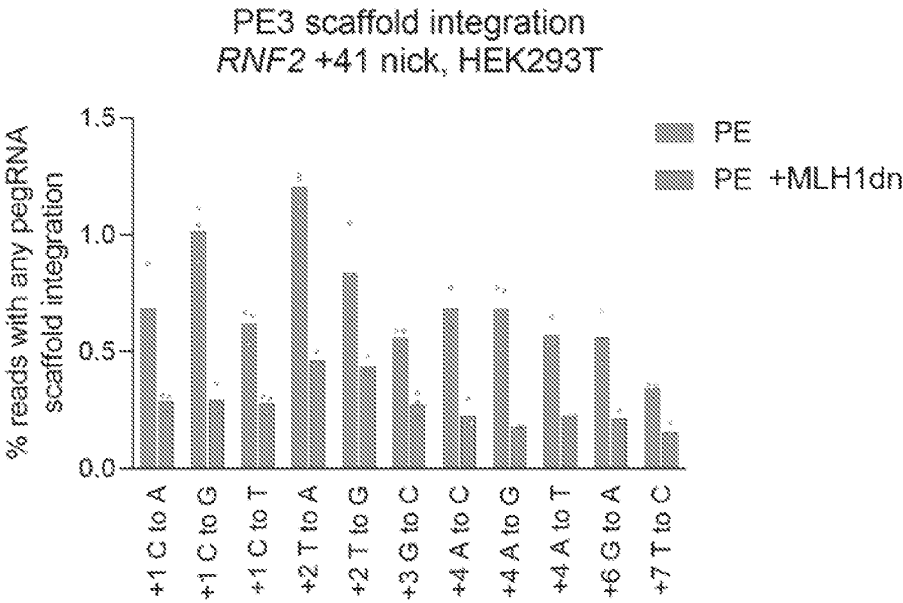


FIG. 26B

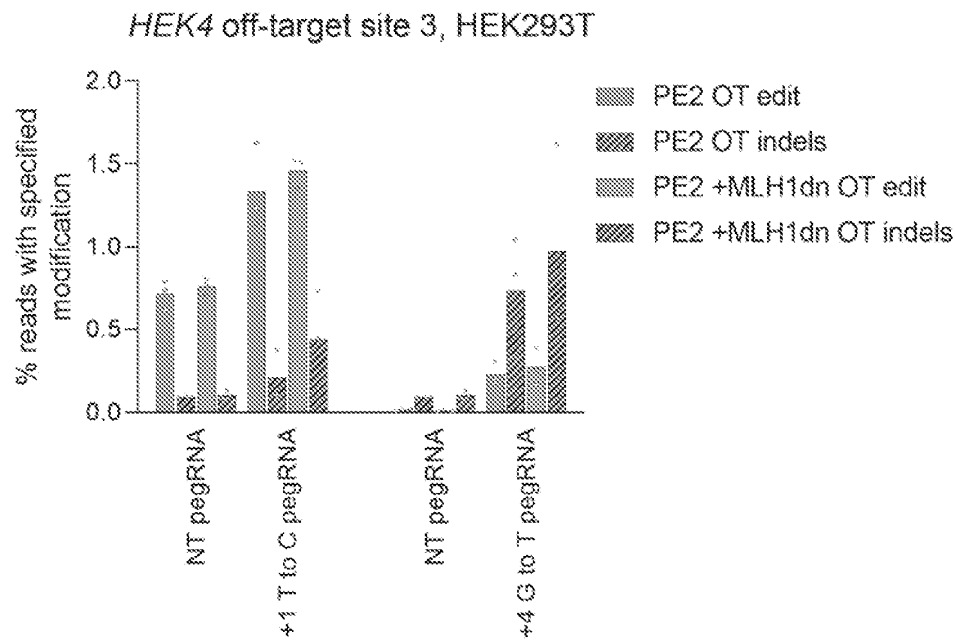


FIG. 27

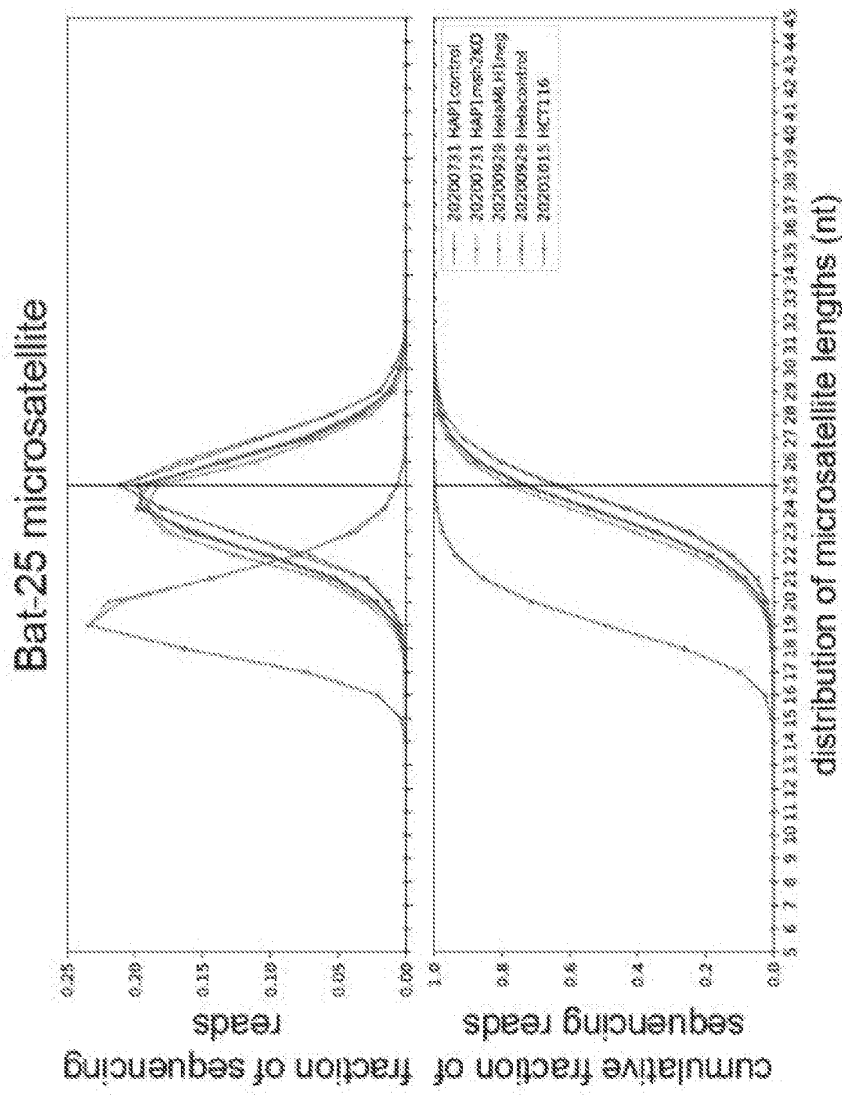


FIG. 28A

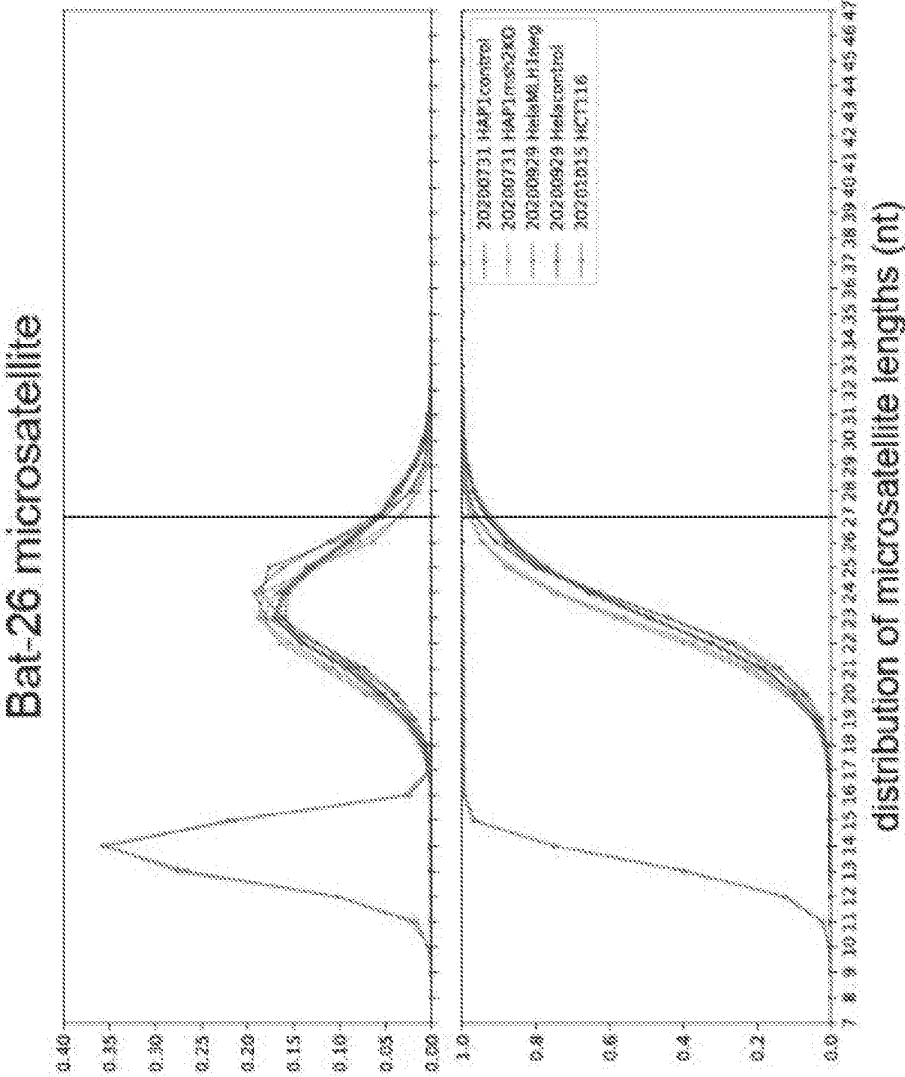


FIG. 28B

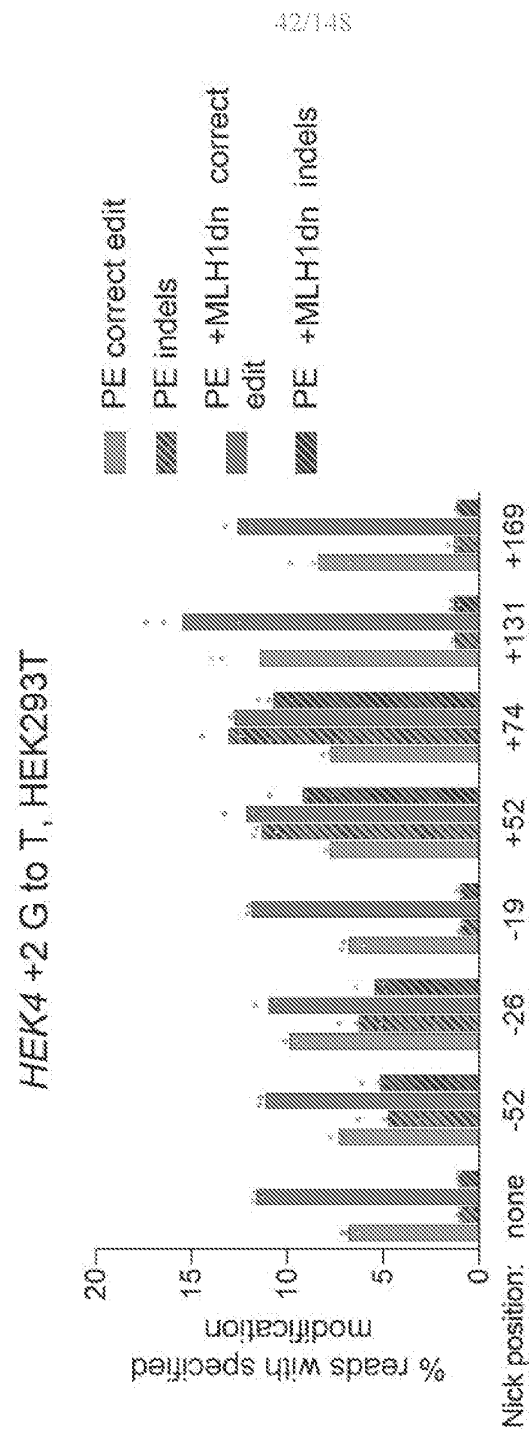


FIG. 29

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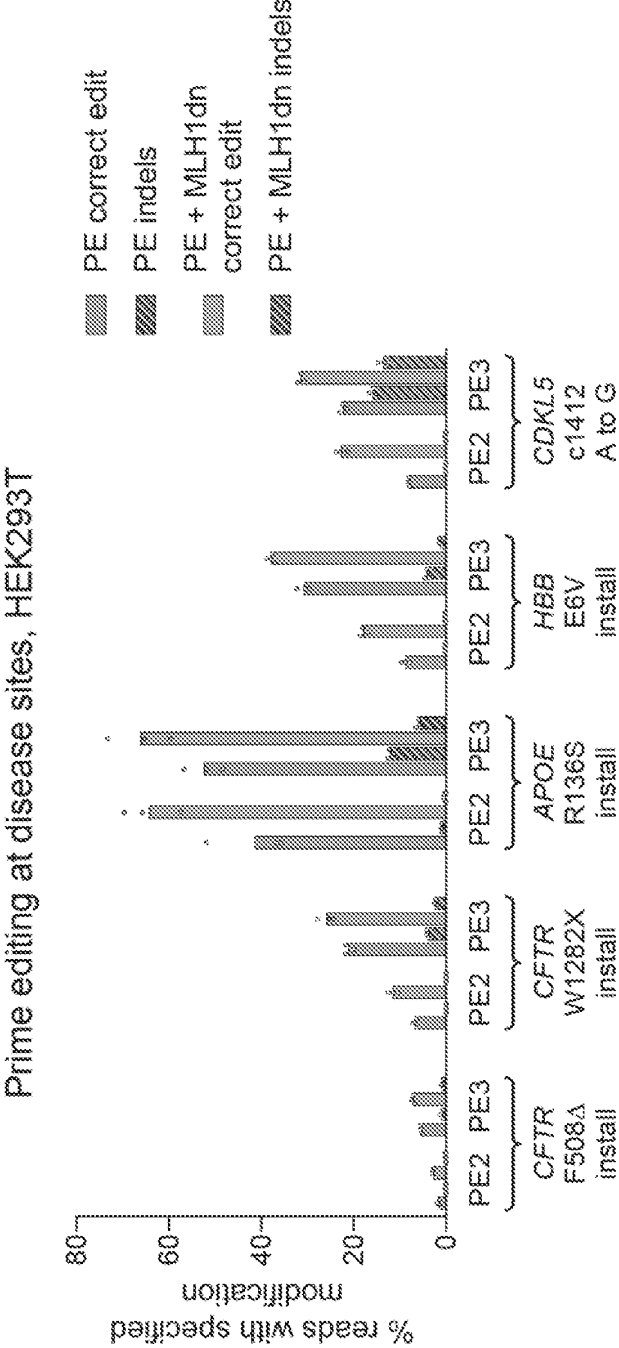


FIG. 30

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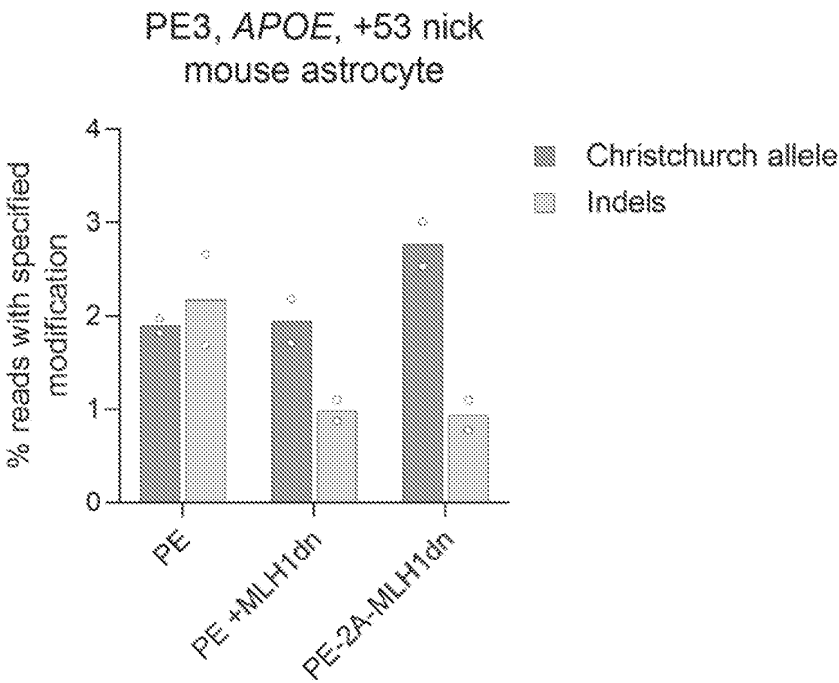


FIG. 31

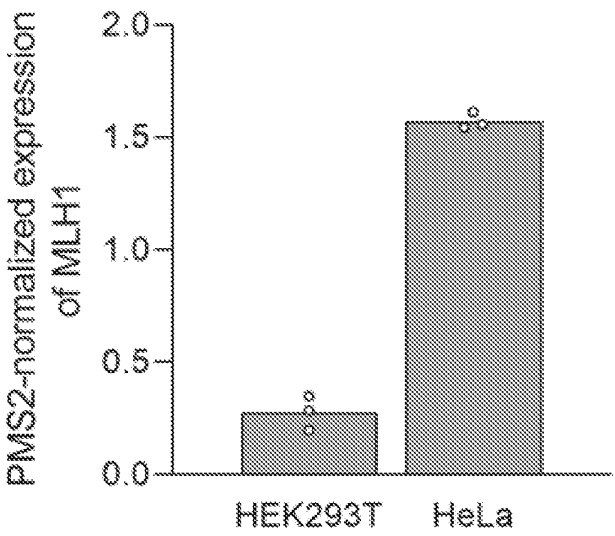


FIG. 32

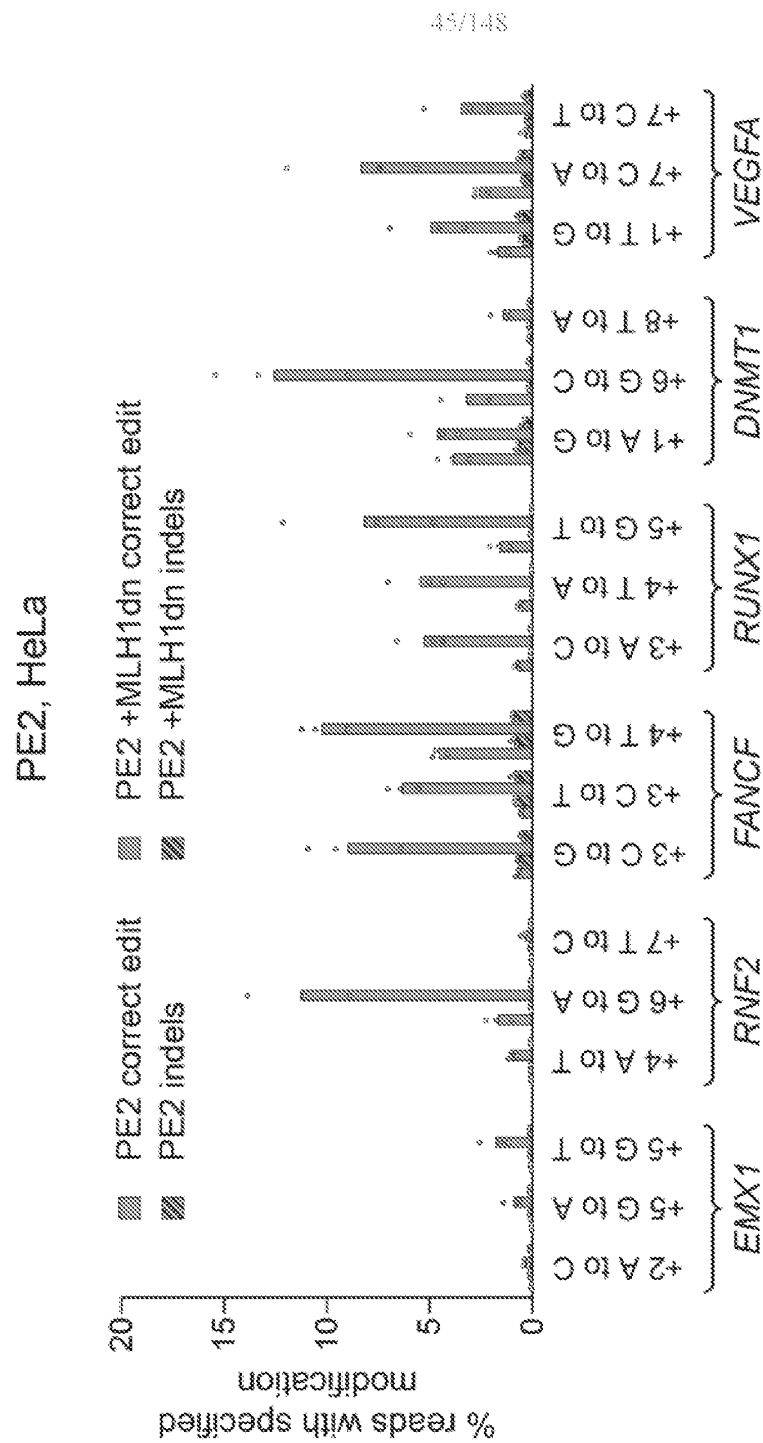


FIG. 33A

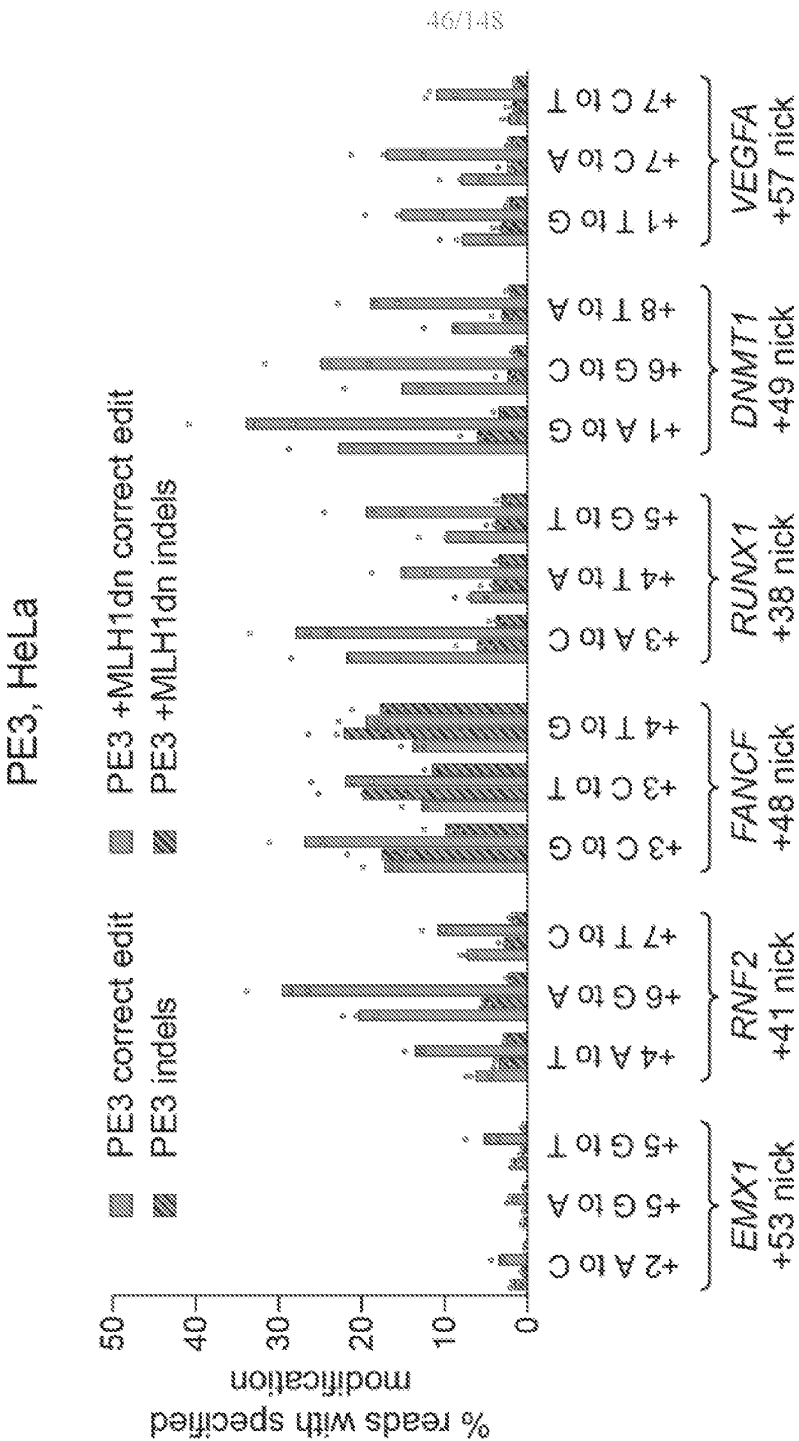


FIG. 33B

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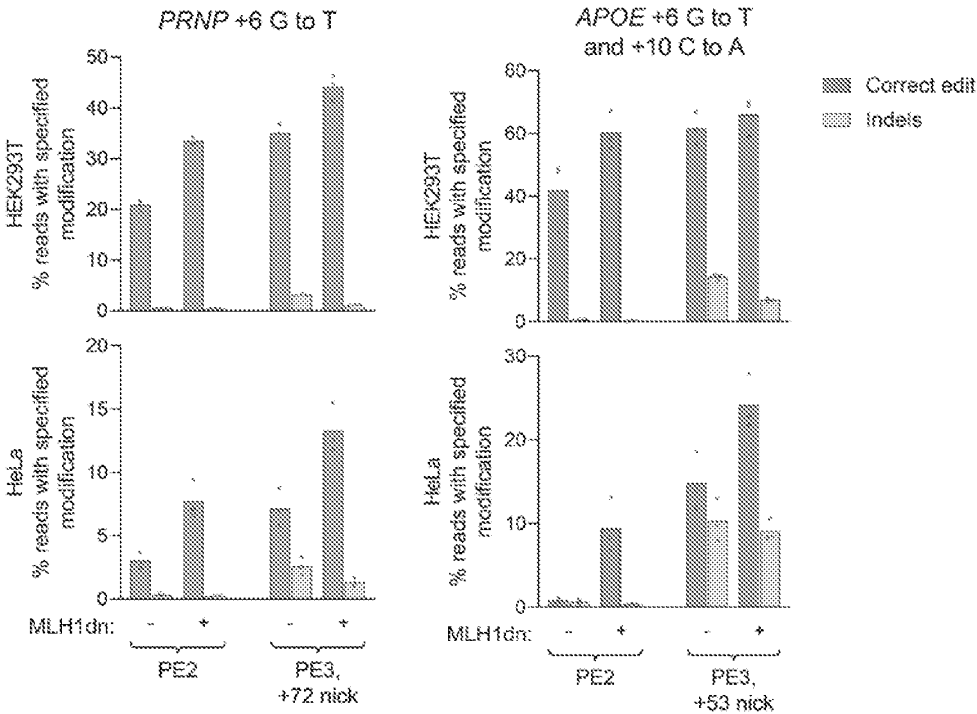


FIG. 34A

FIG. 34B

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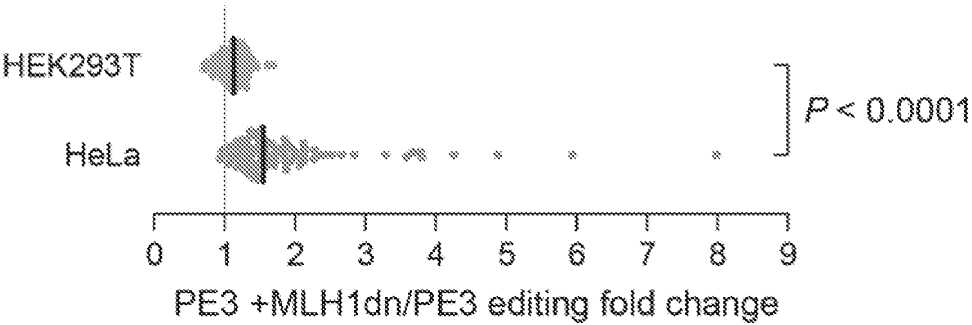


FIG. 35A

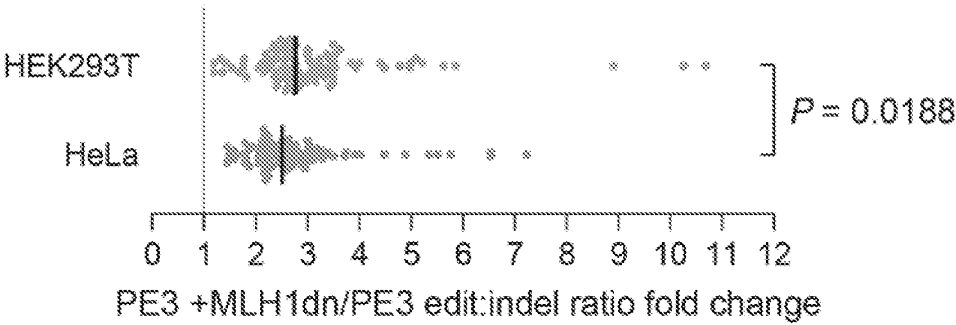


FIG. 35B

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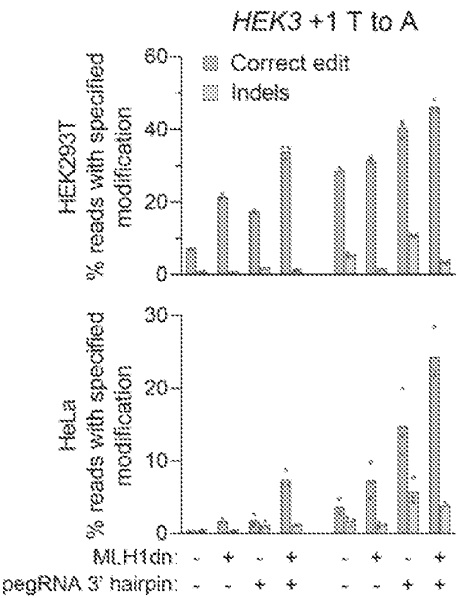


FIG. 36A

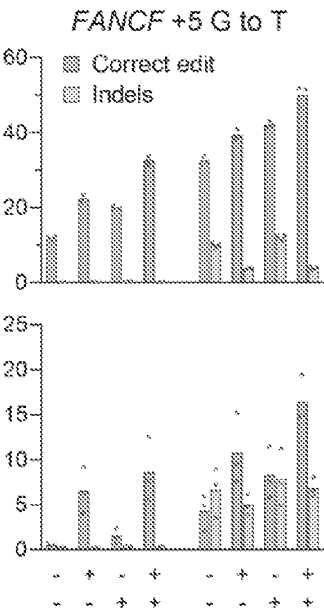


FIG. 36B

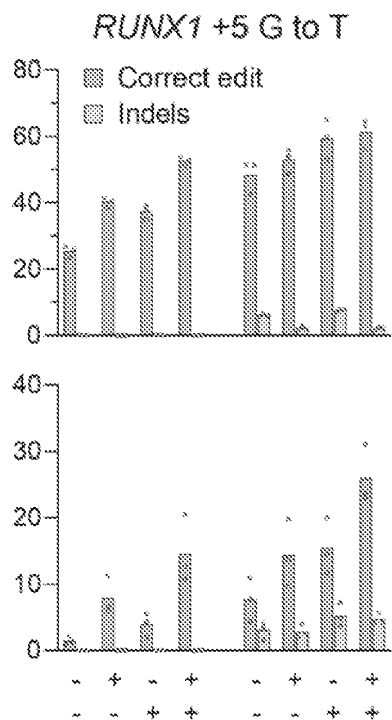


FIG. 36C

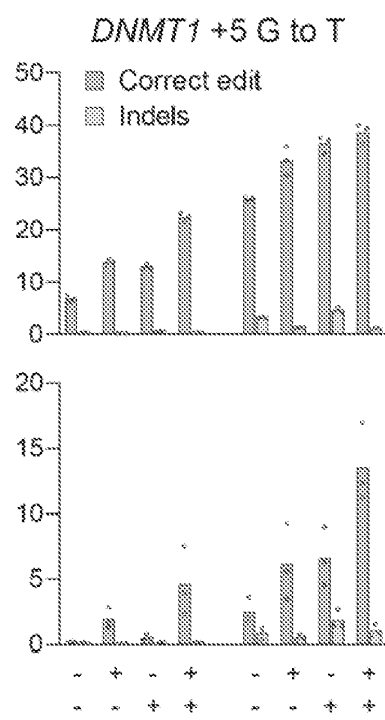


FIG. 36D

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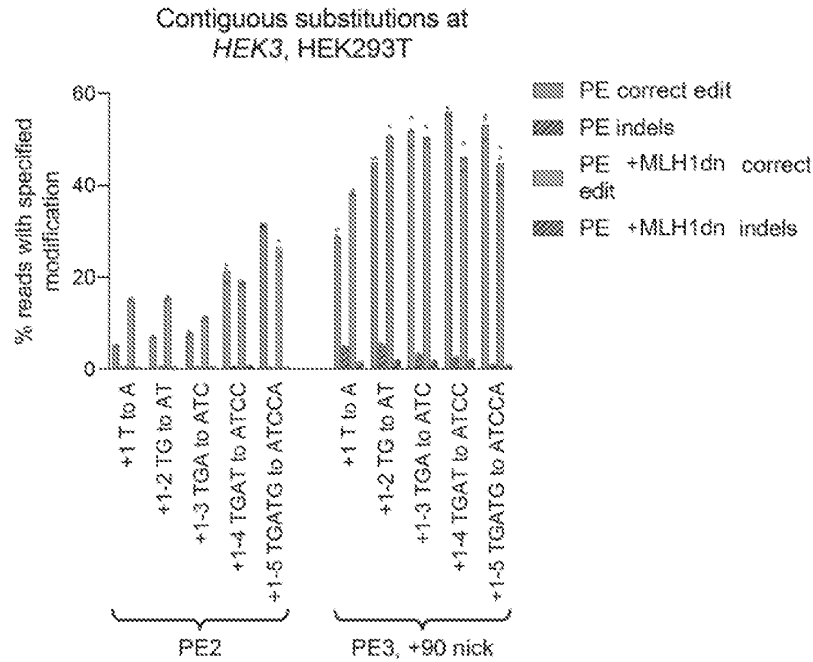


FIG. 37A

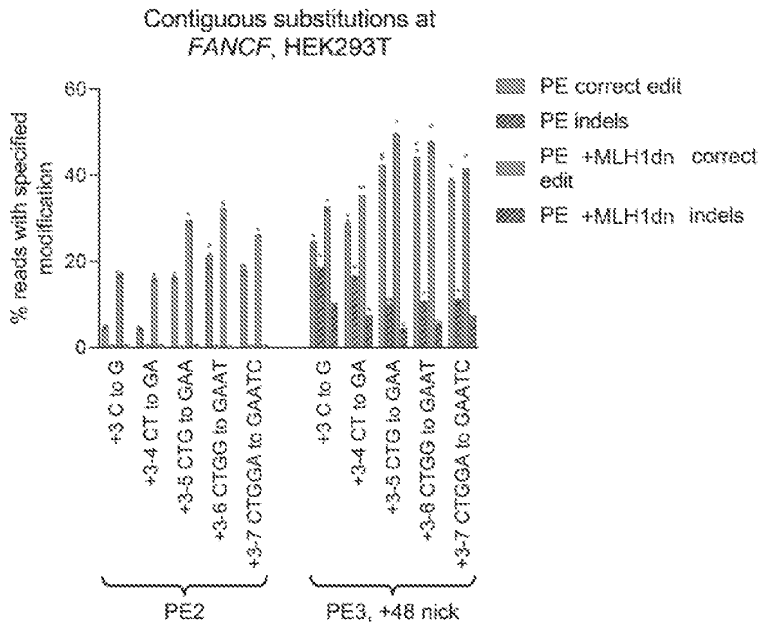


FIG. 37B

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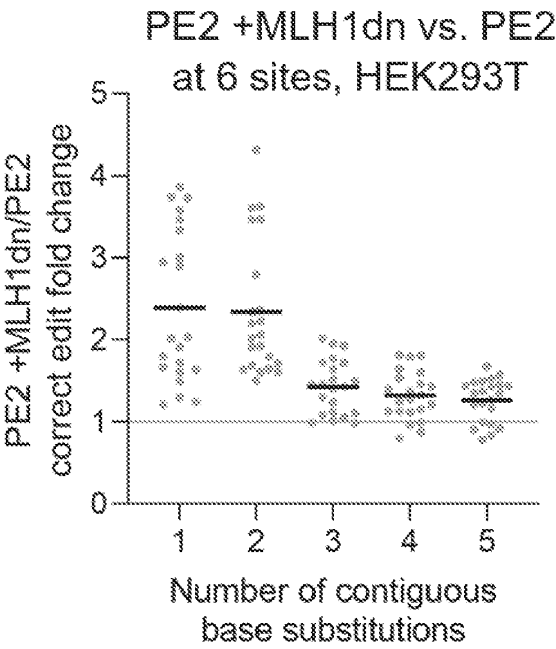


FIG. 38

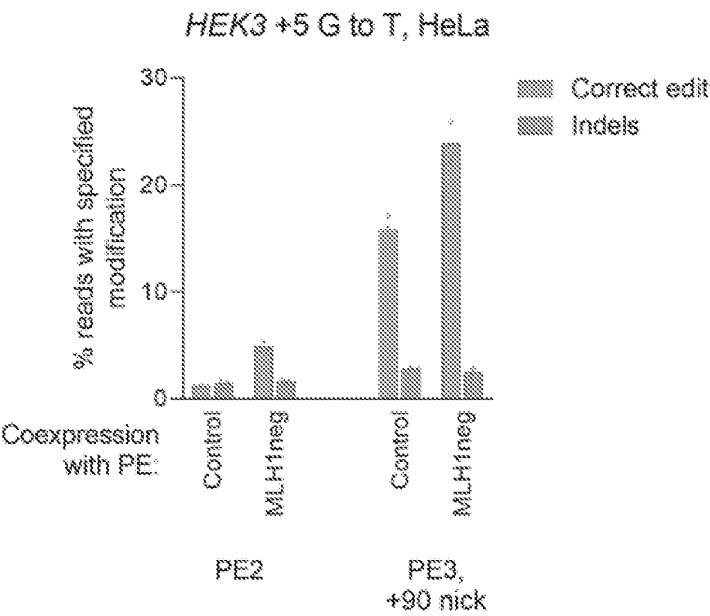
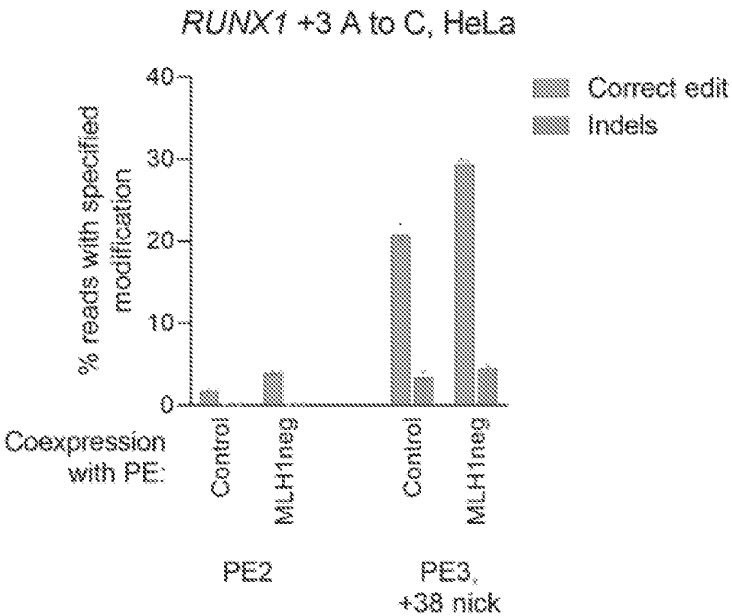
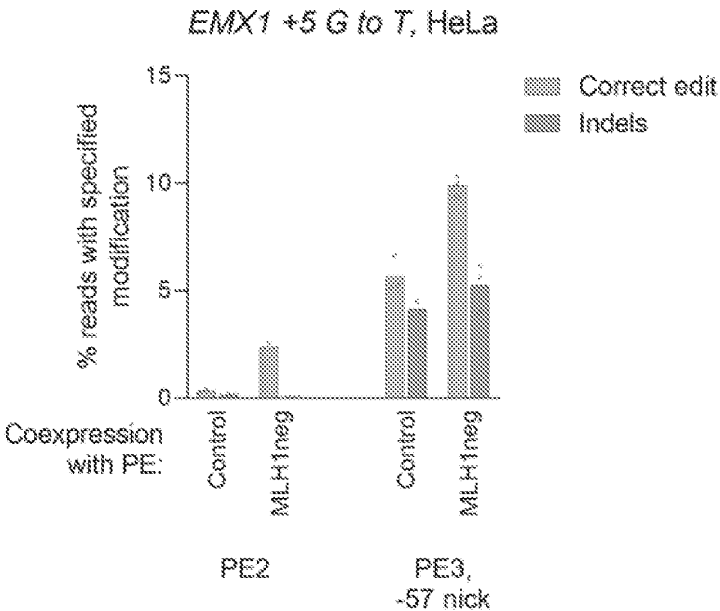


FIG. 39A

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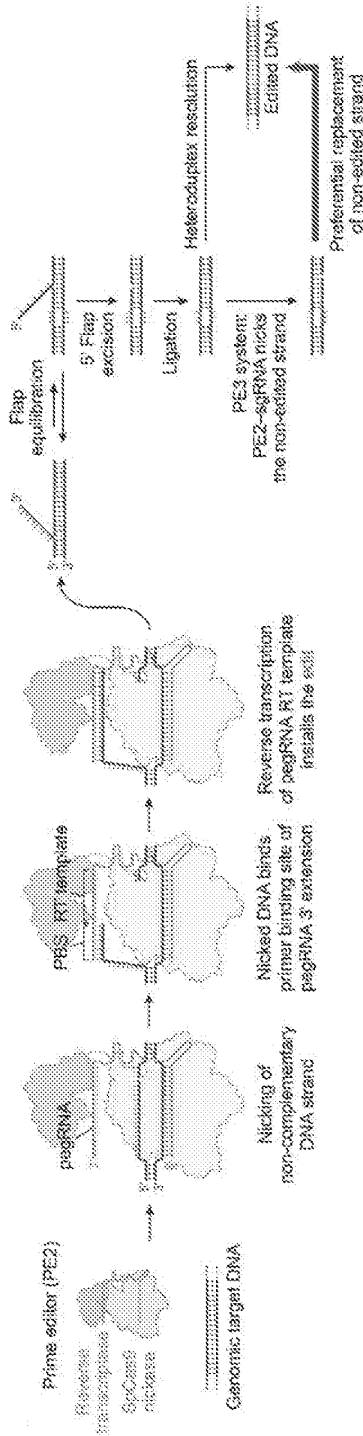


FIG. 40A

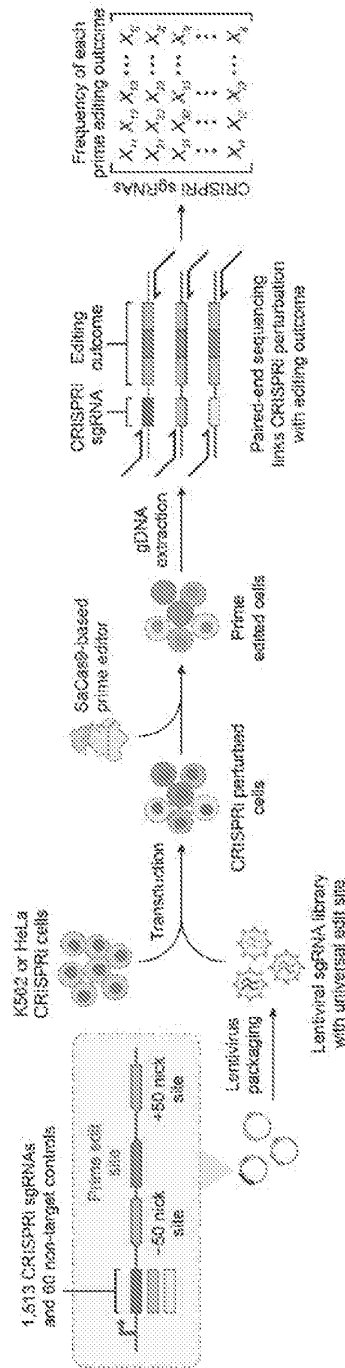


FIG. 40B

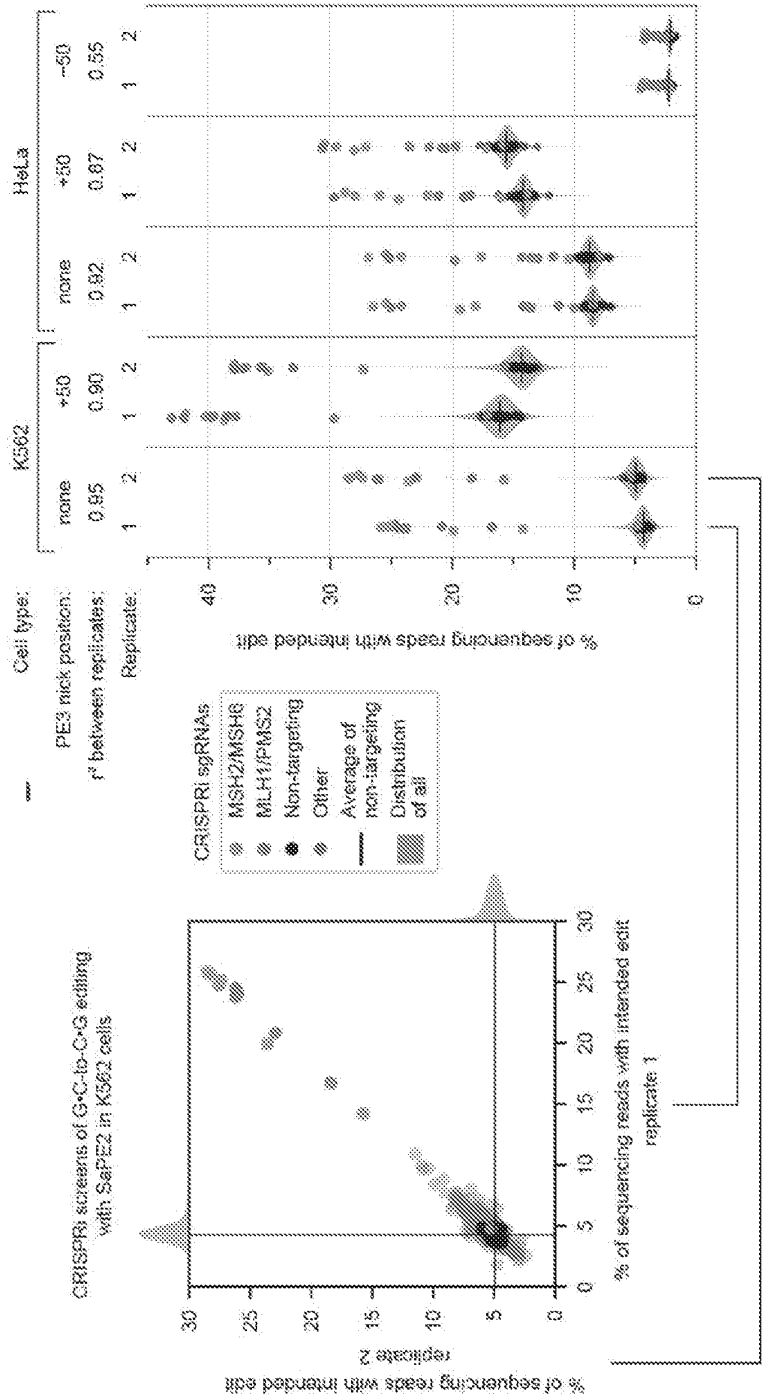
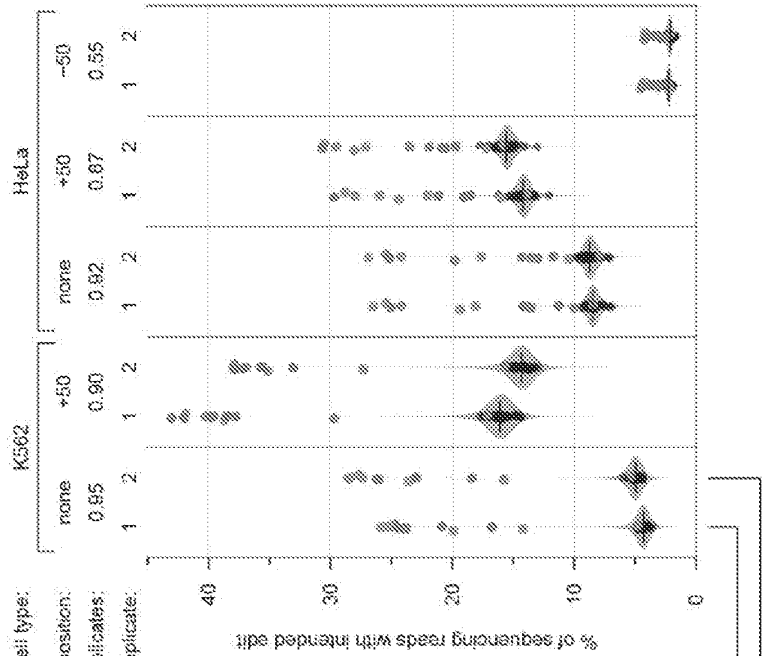


FIG. 40D



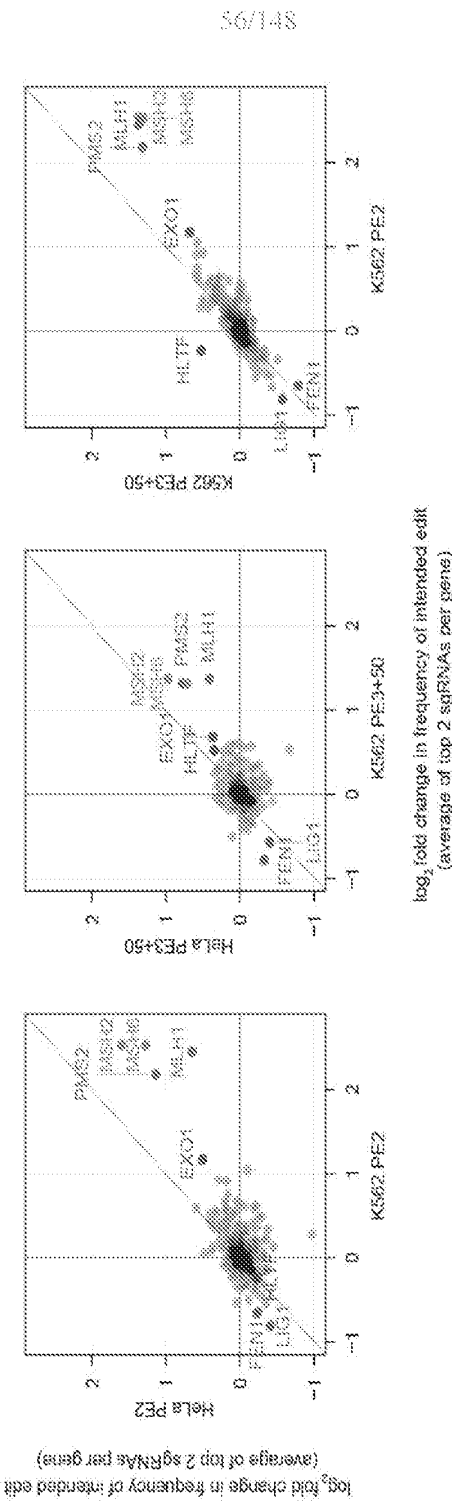


FIG. 40E

FIG. 40F

FIG. 40G

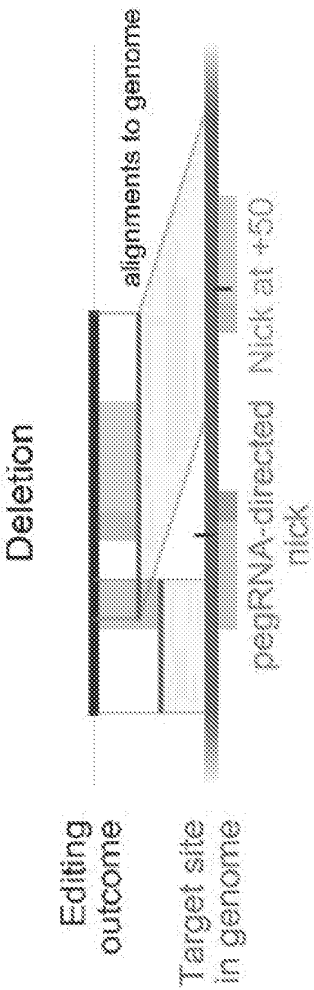


FIG. 41A

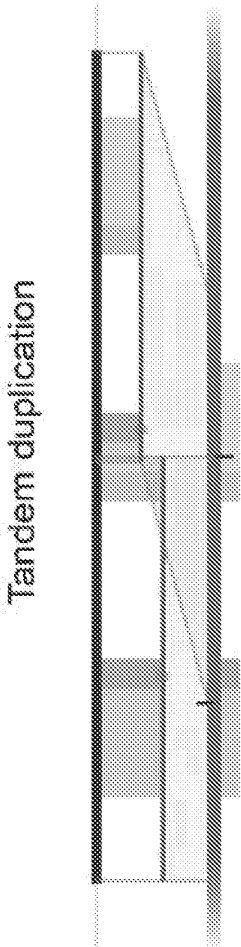


FIG. 41B

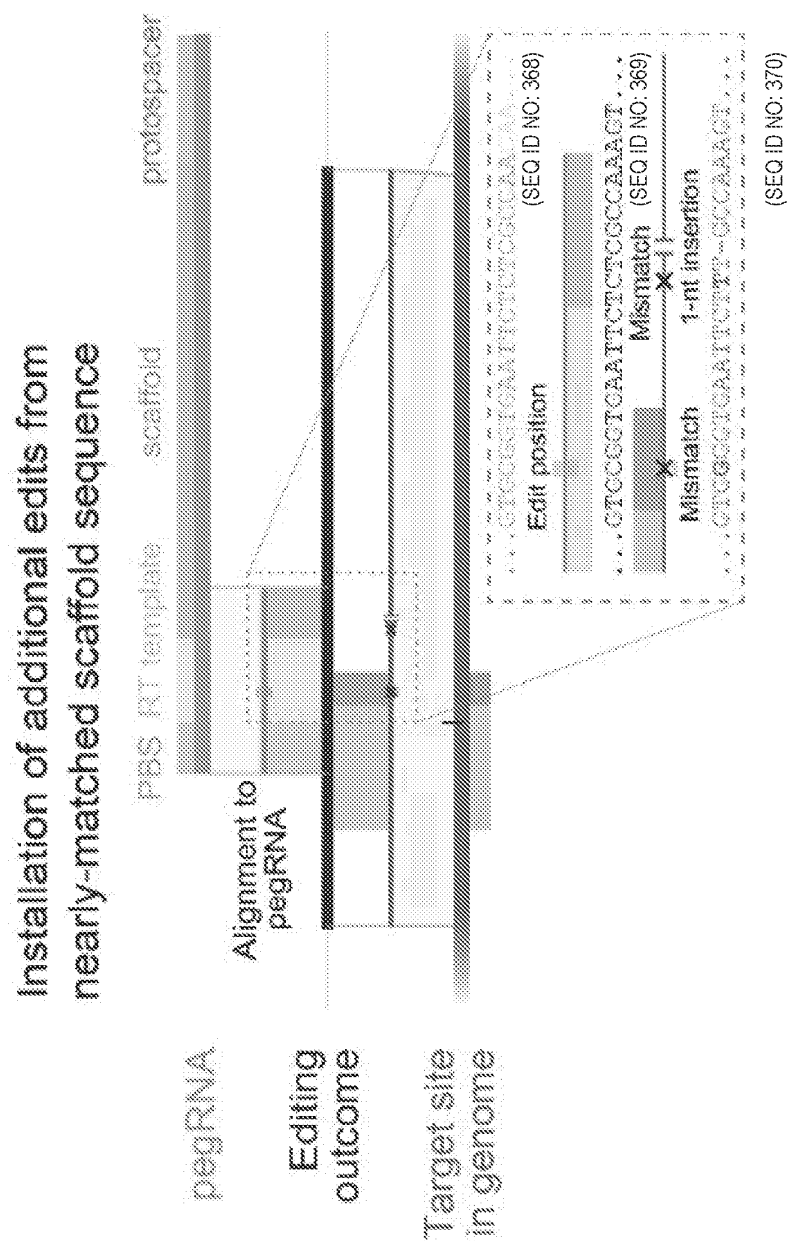


FIG. 41C

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Joining of reverse transcribed
sequence at unintended location

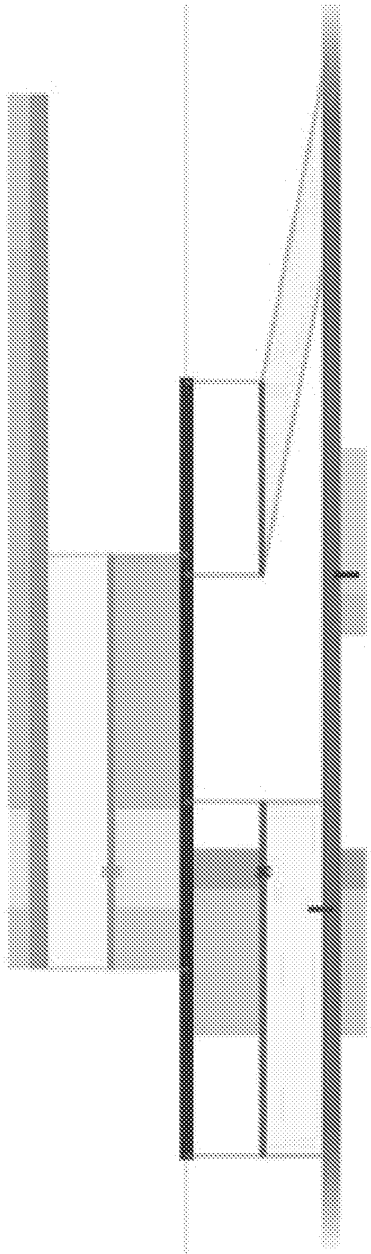


FIG. 41D

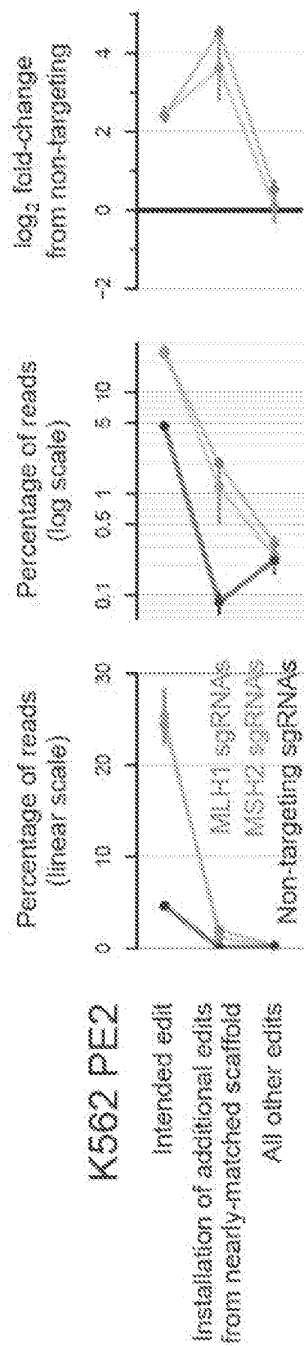


FIG. 41E

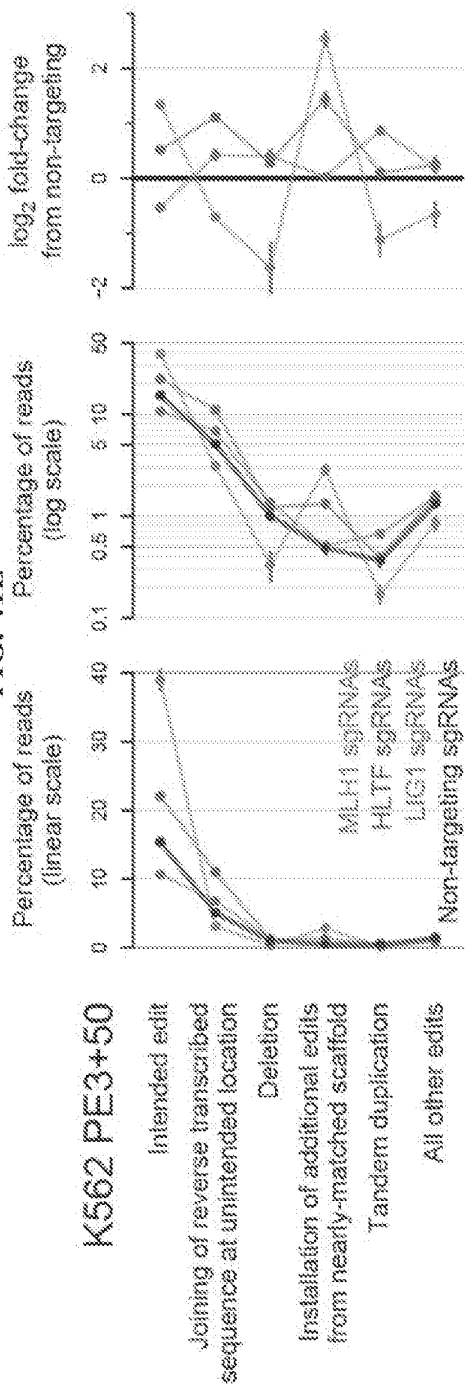
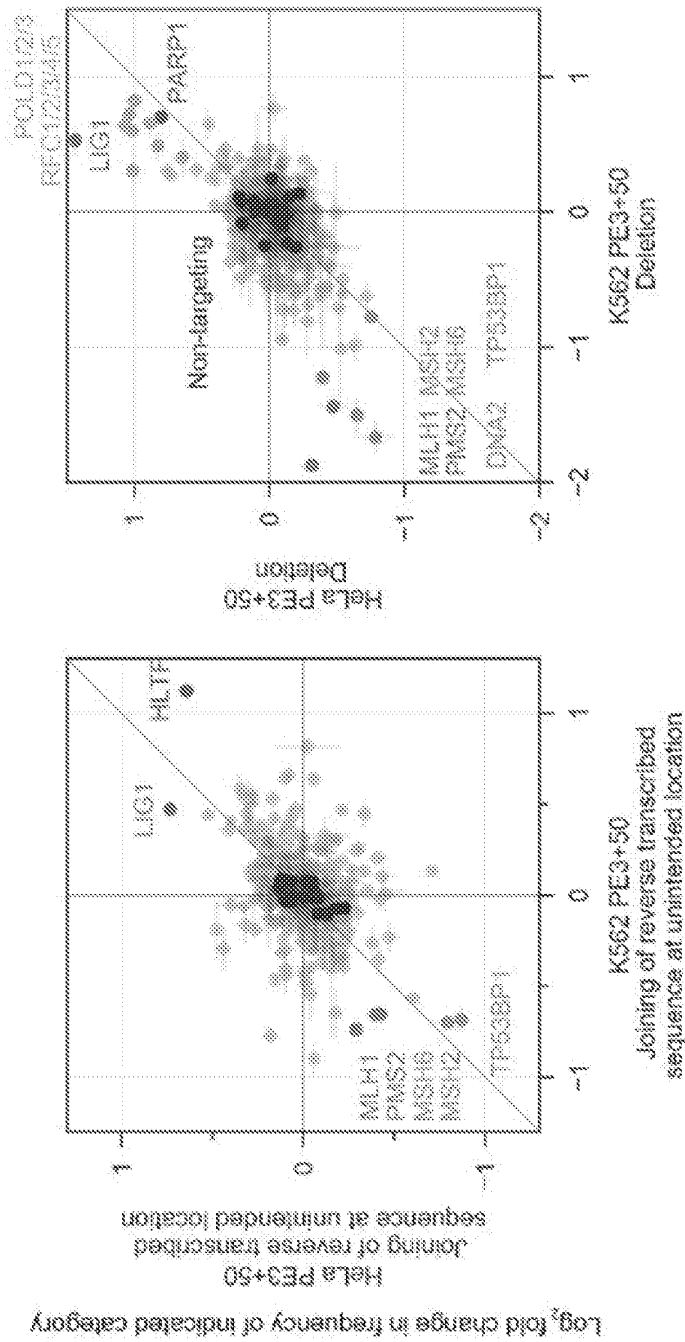


FIG. 41F



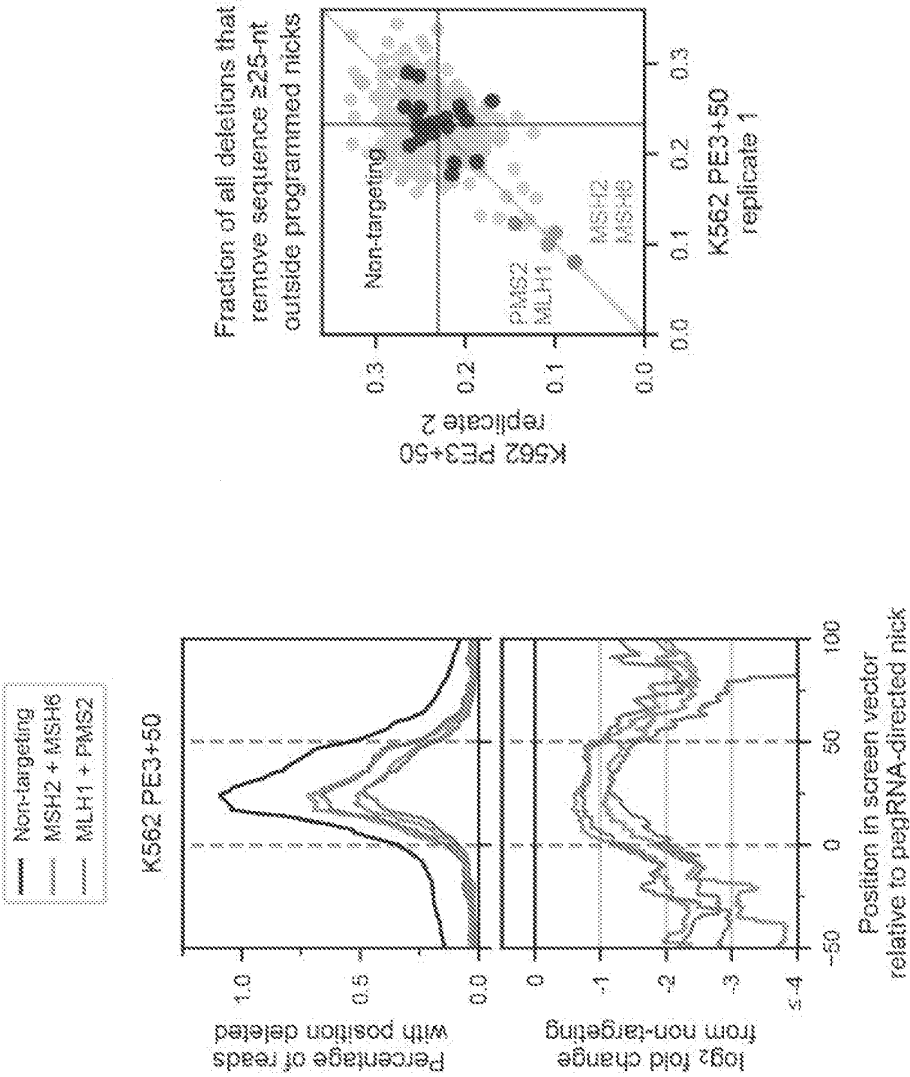


FIG. 4IJ

FIG. 4II

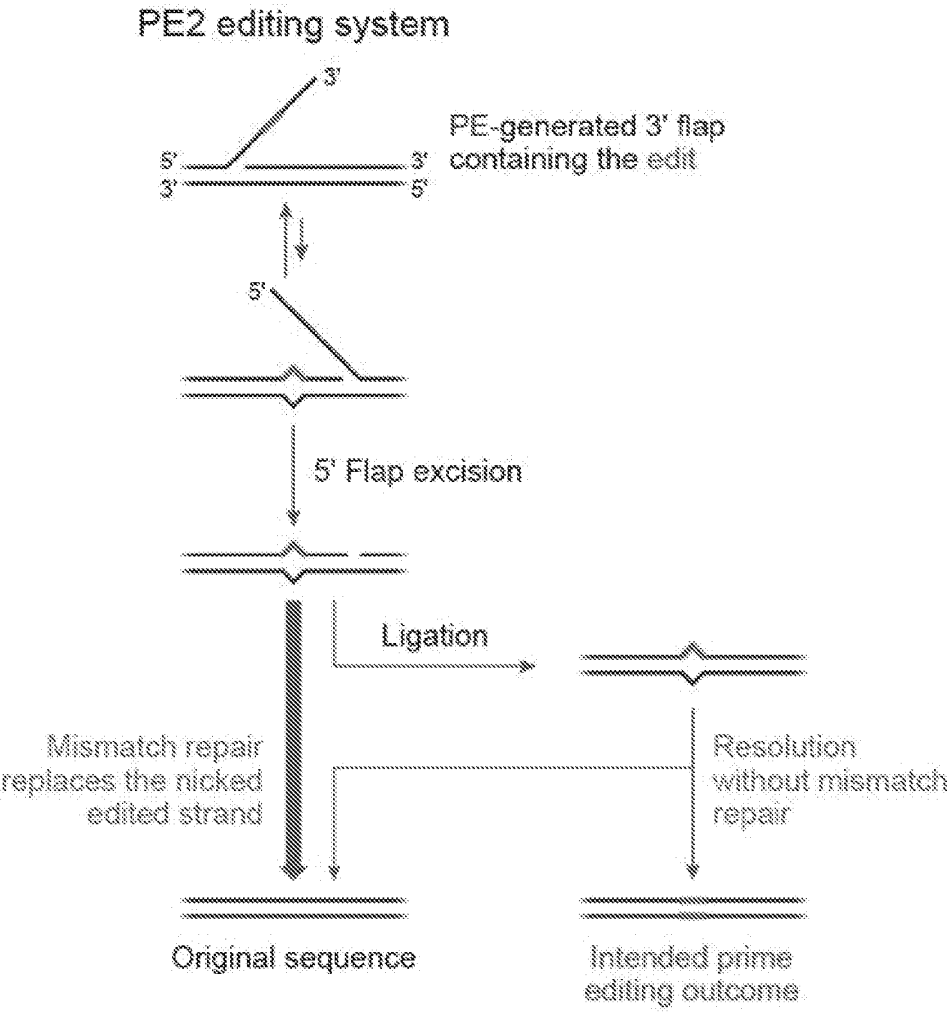


FIG. 42A

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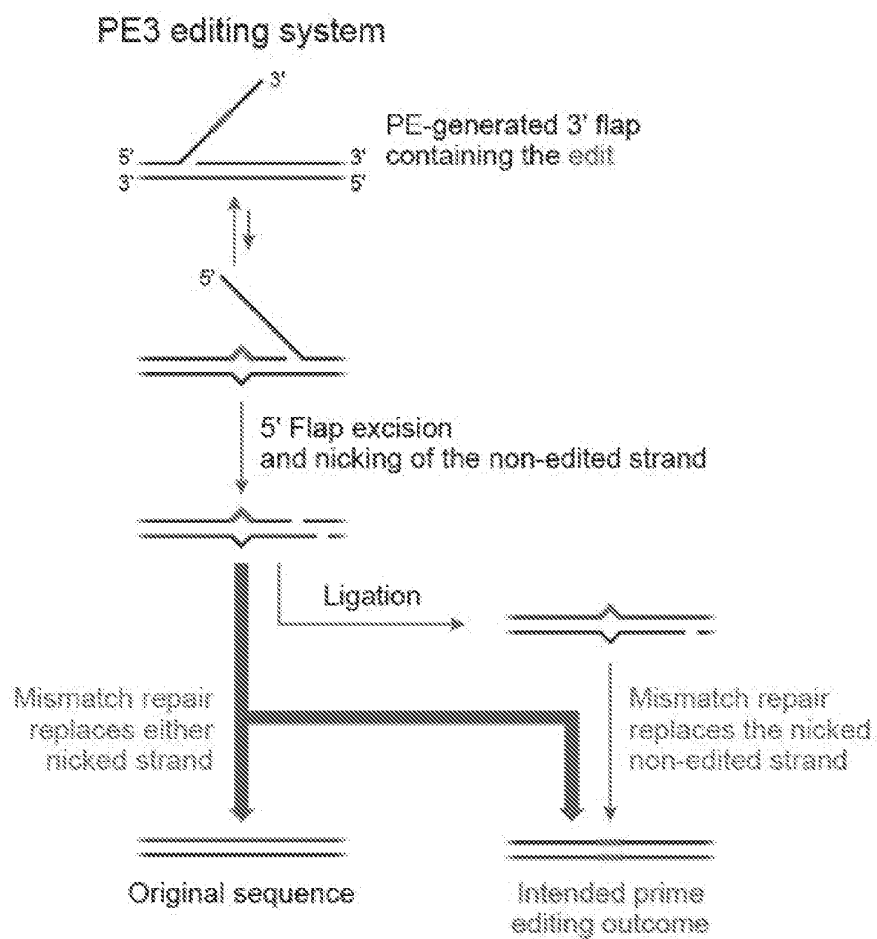


FIG. 42B

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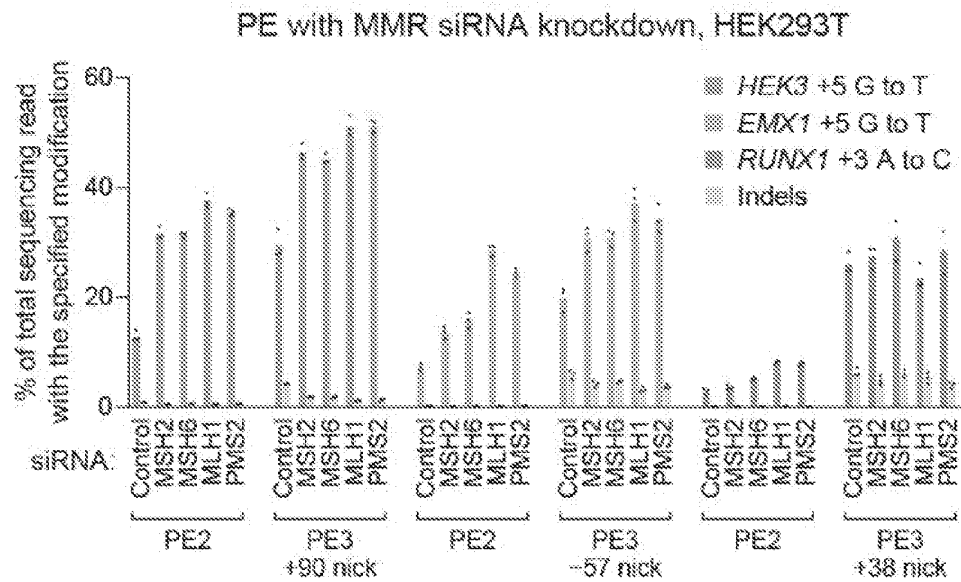


FIG. 42C

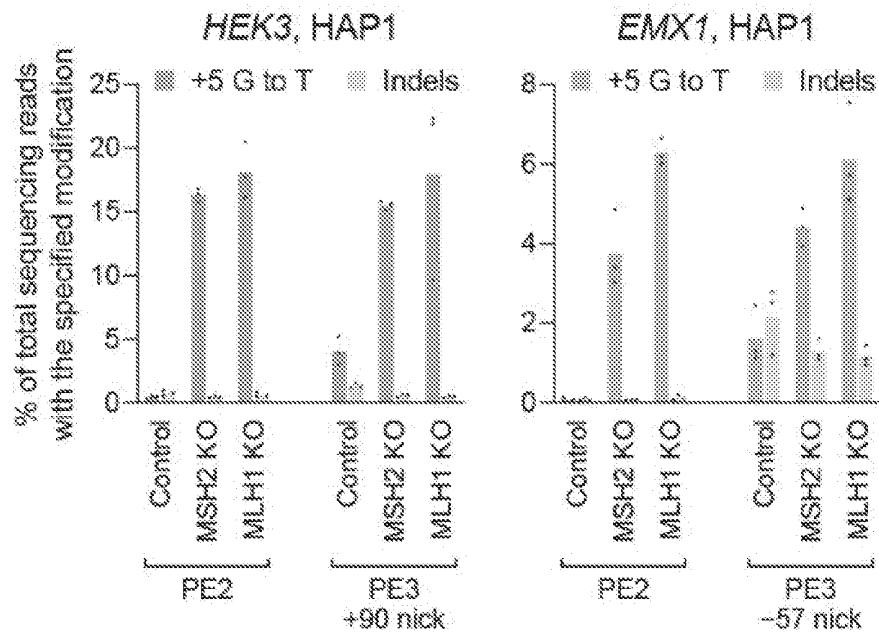


FIG. 42D

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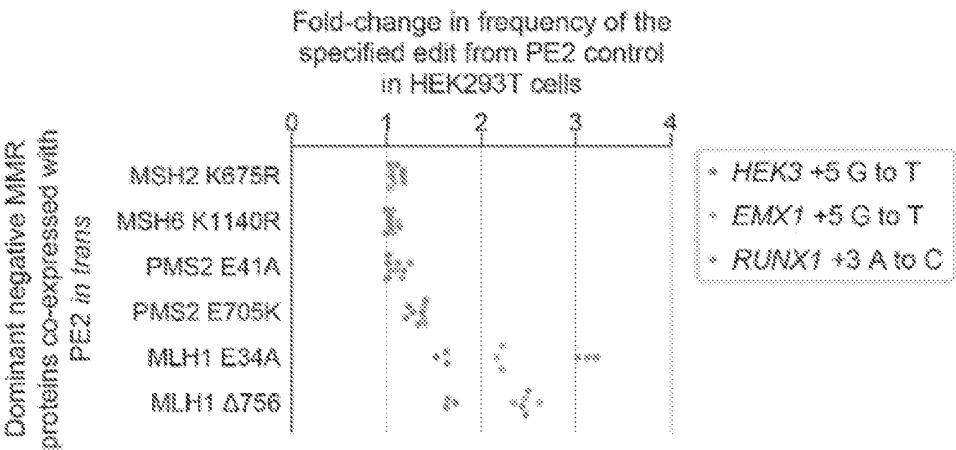


FIG. 43A

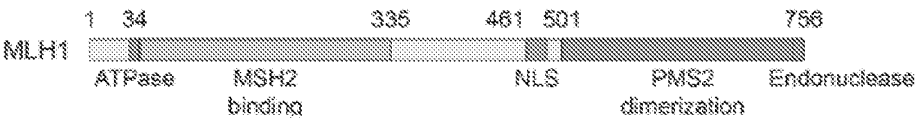


FIG. 43B

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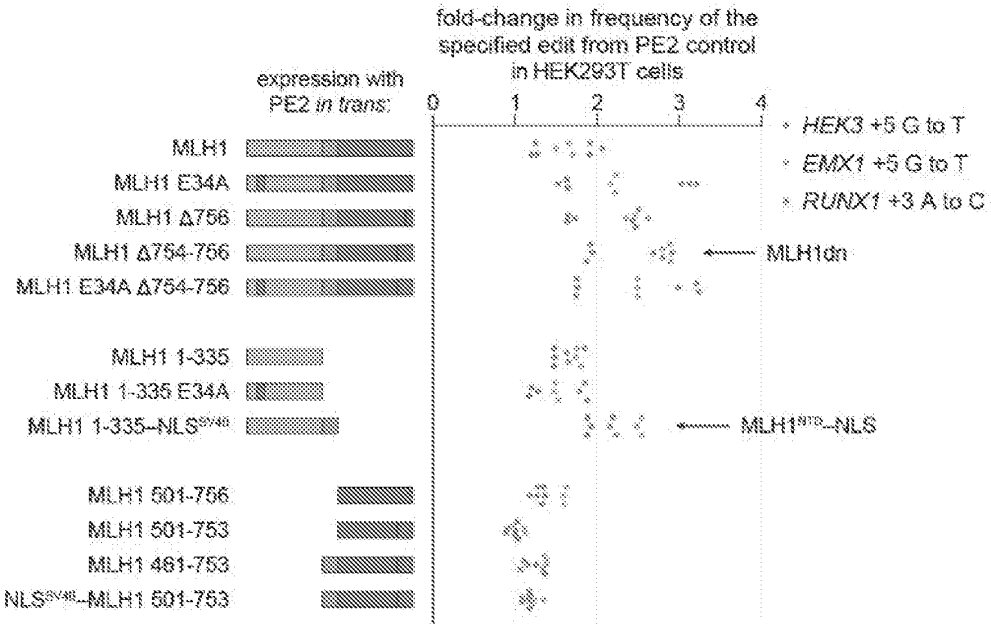


FIG. 43C

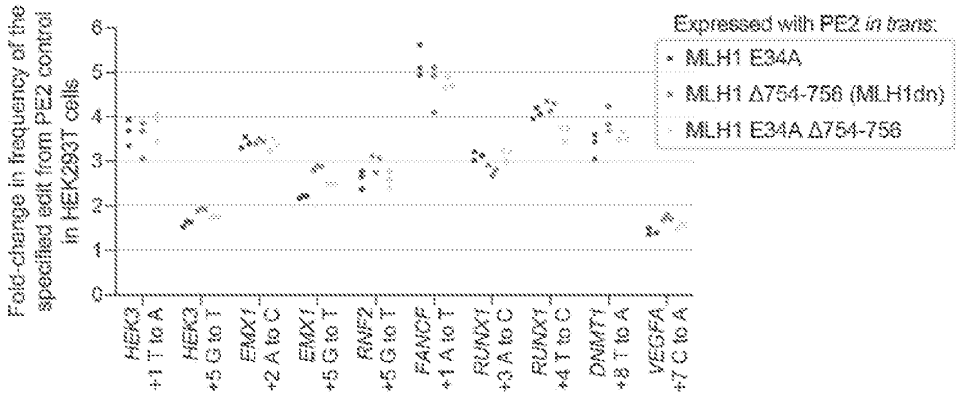


FIG. 43D

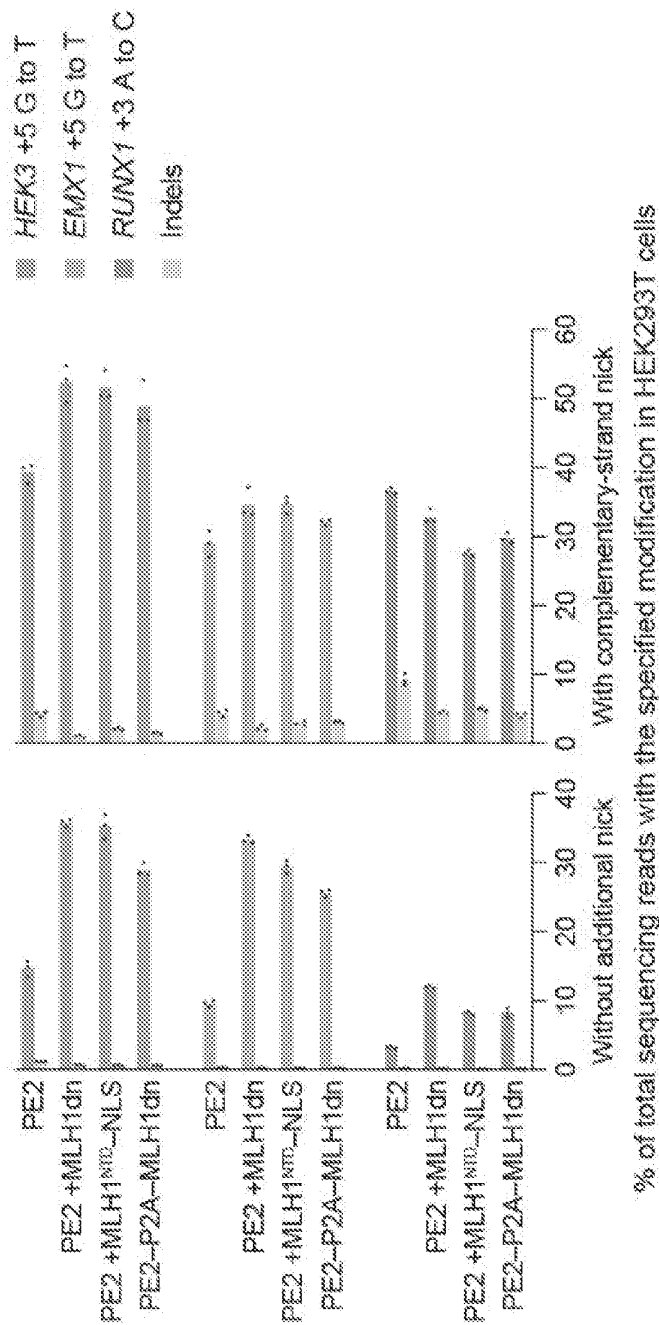


FIG. 43E

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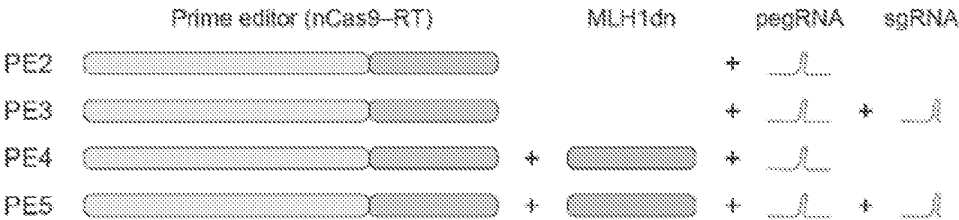


FIG. 43F

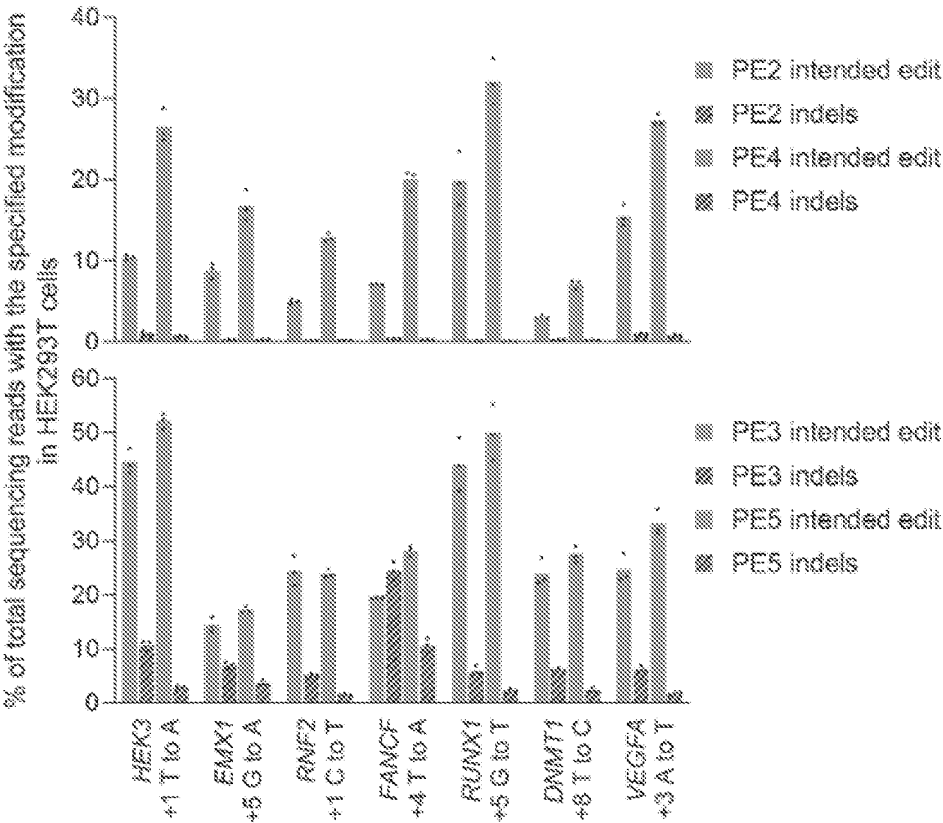


FIG. 43G

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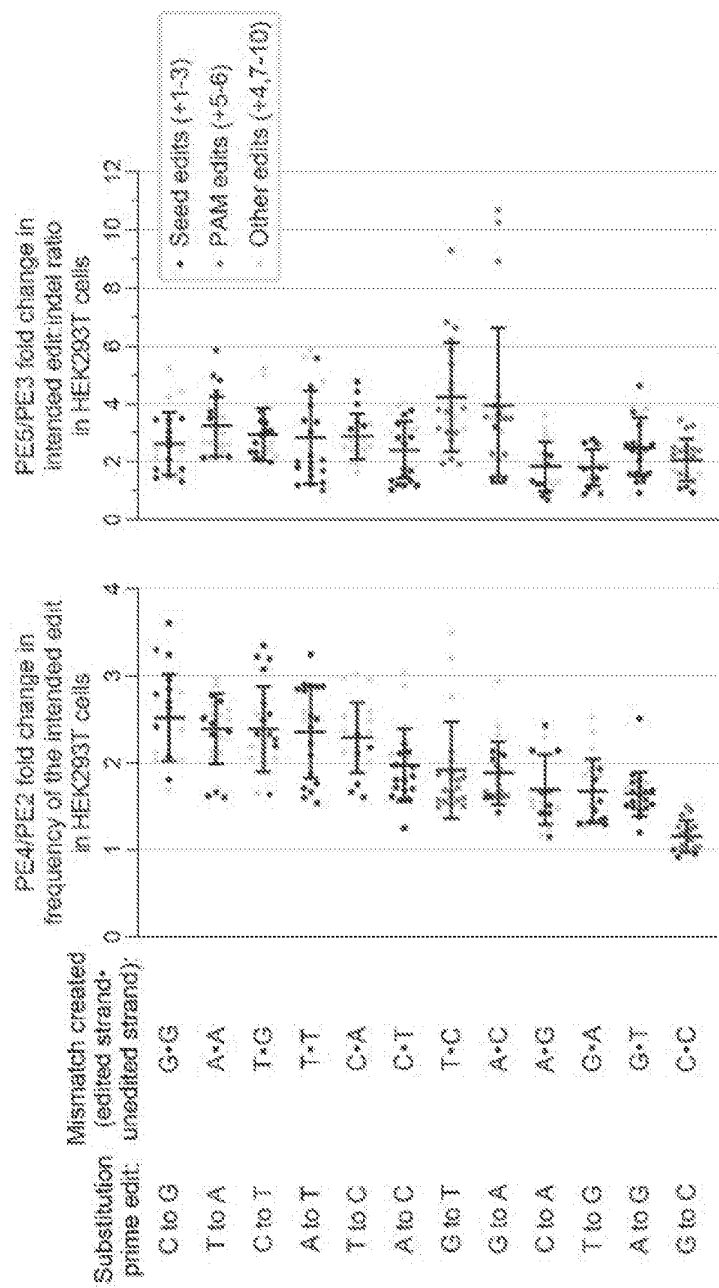


FIG. 44A

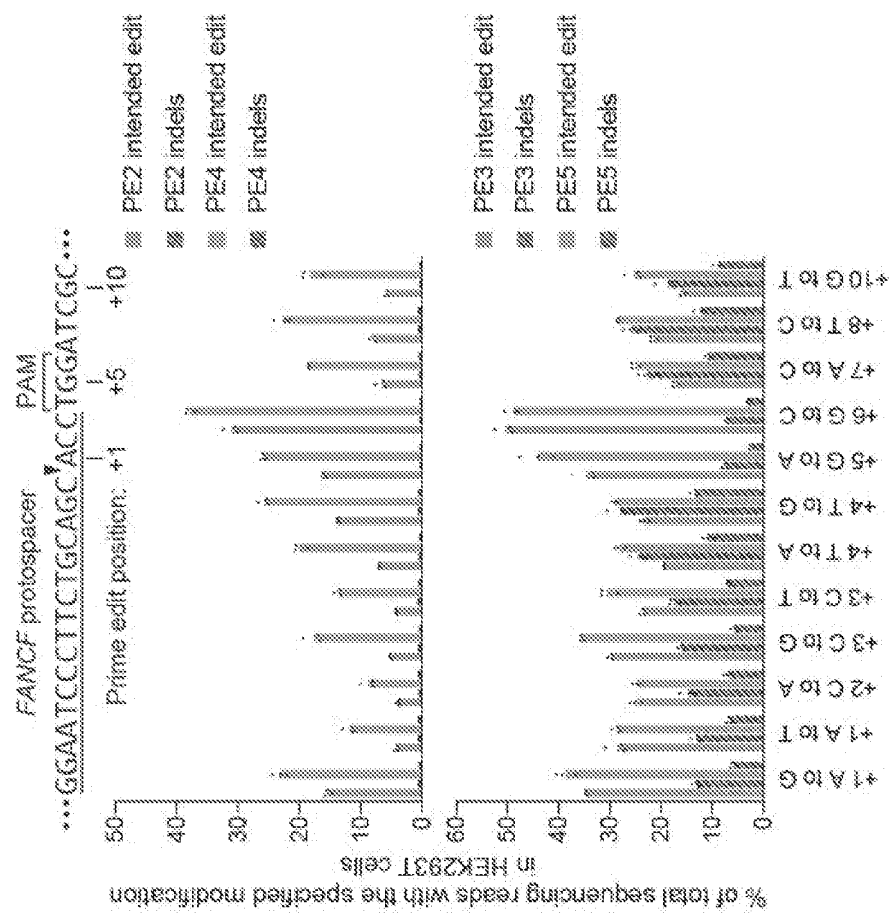


FIG. 44B

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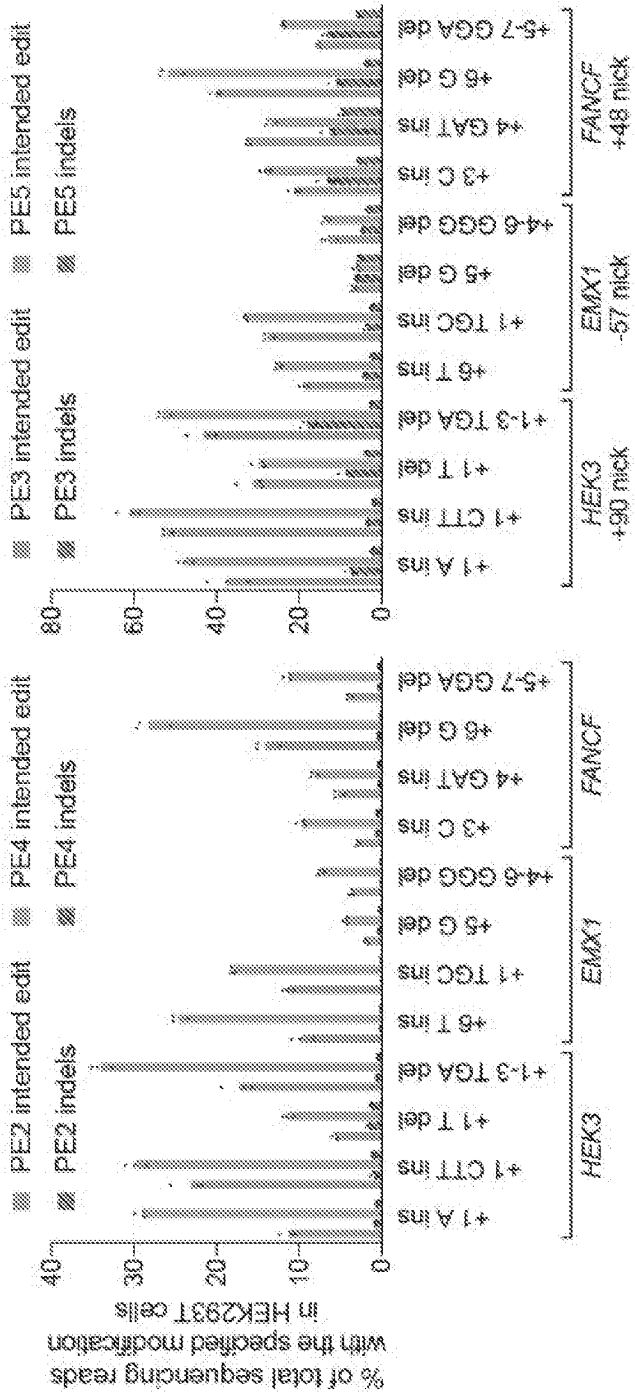


FIG. 44C

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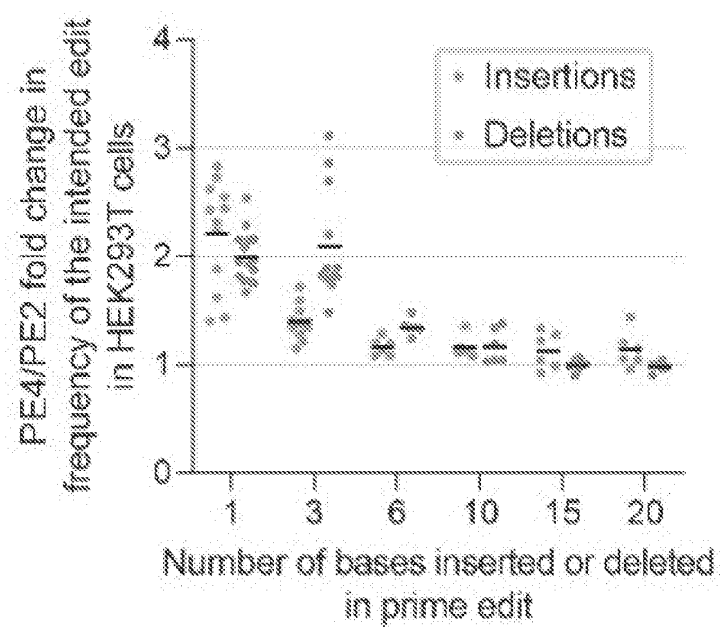


FIG. 44D

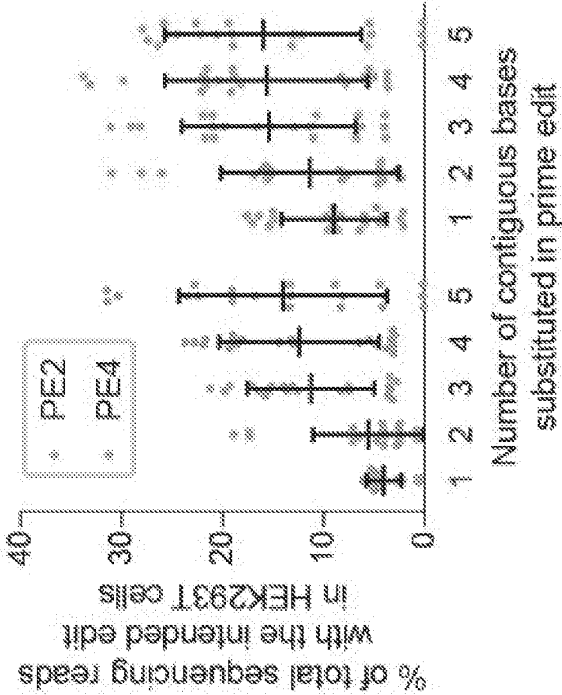


FIG. 44F

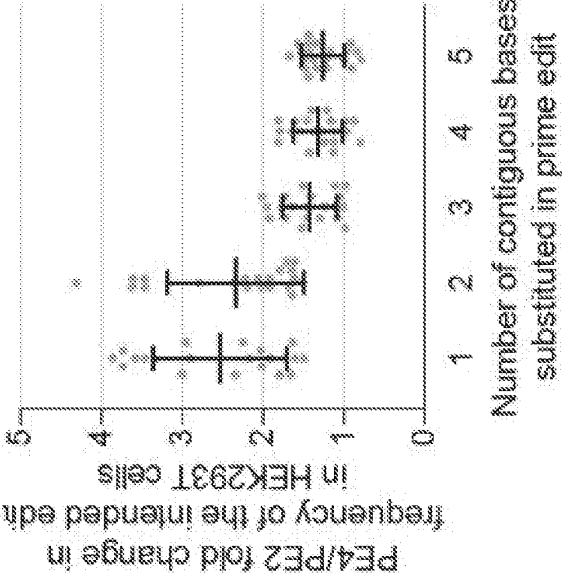


FIG. 44E

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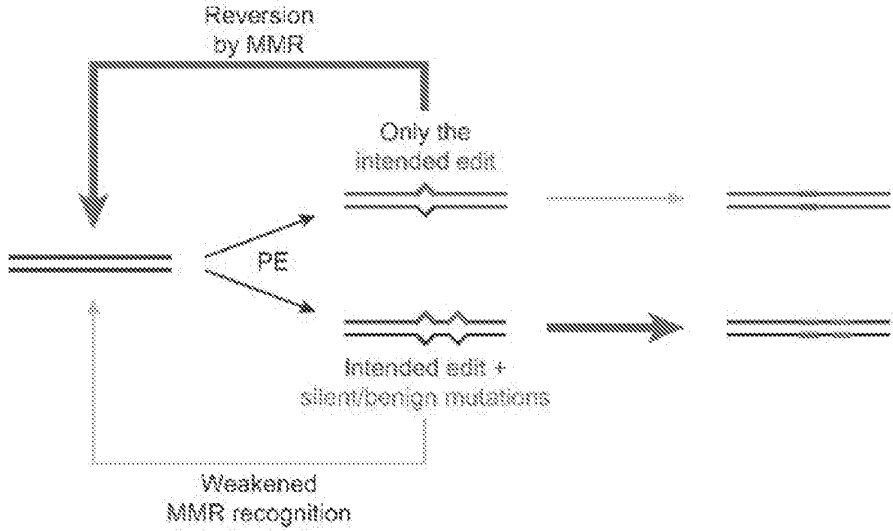


FIG. 44G

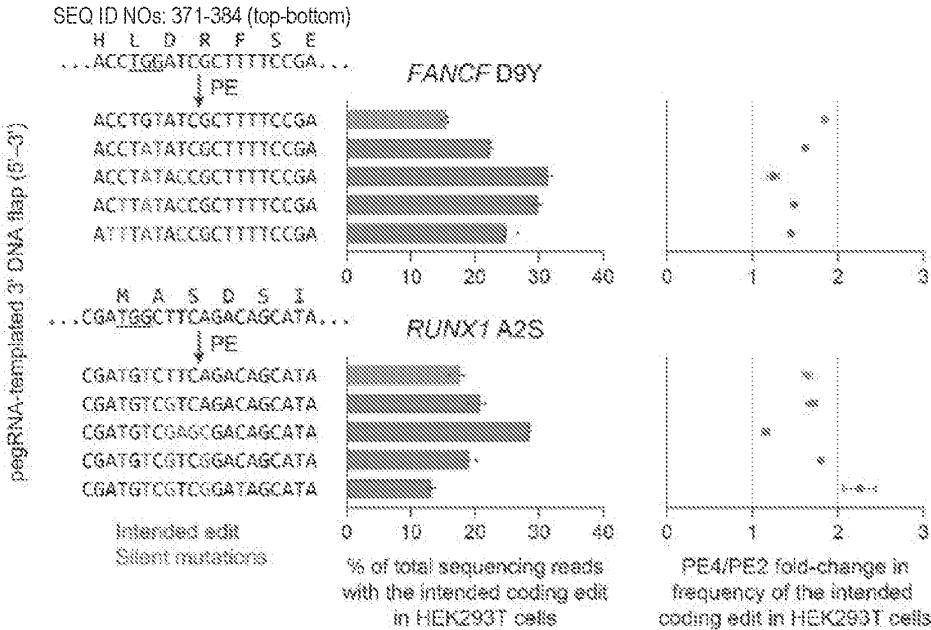


FIG. 44H

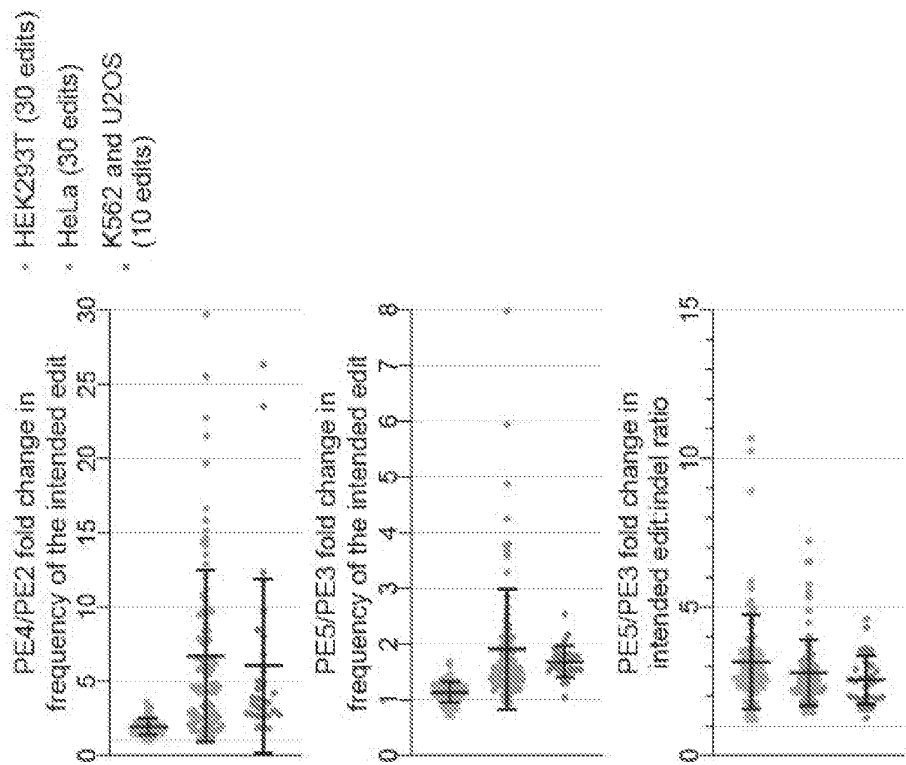


FIG. 44I

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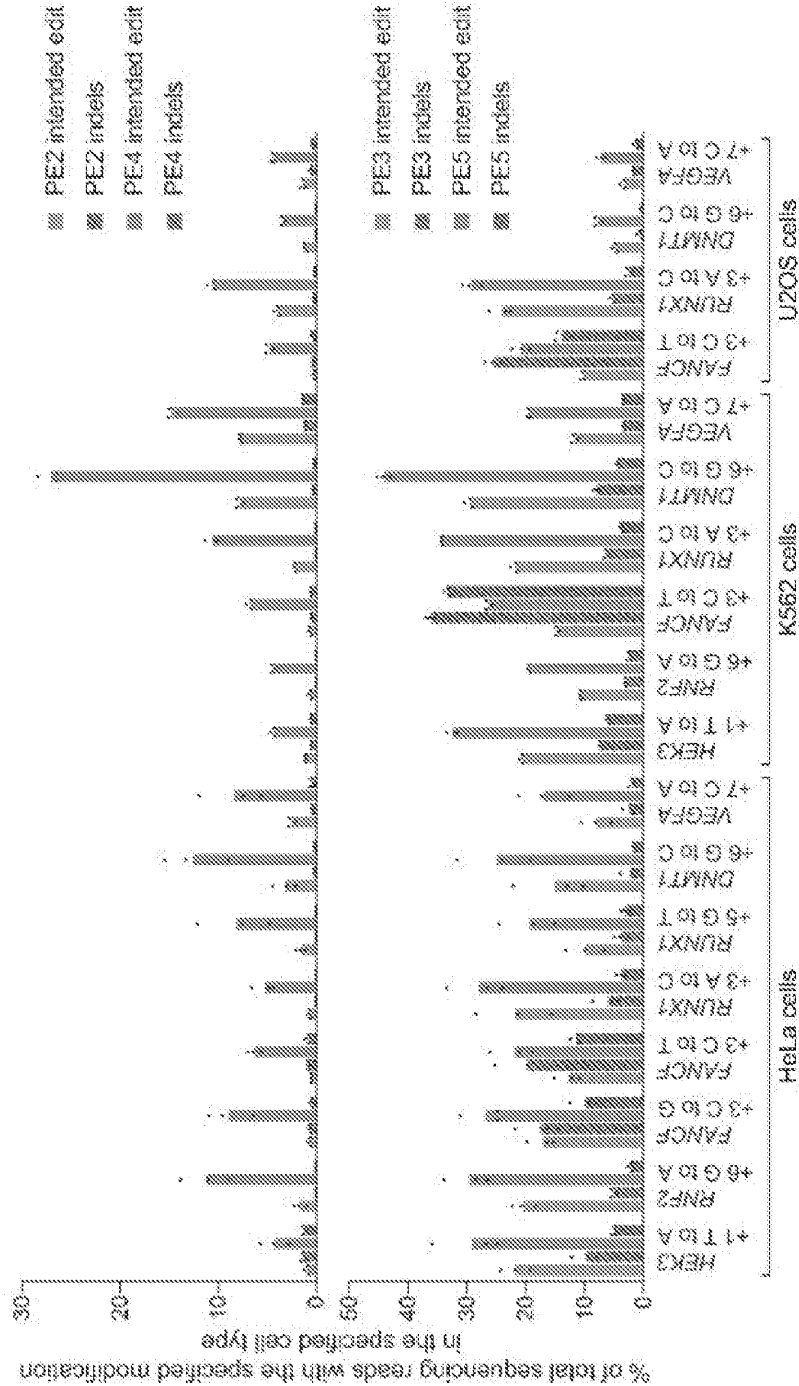


FIG. 44J

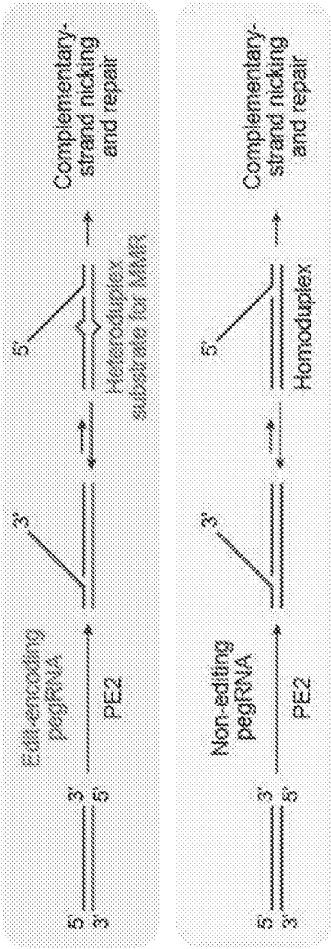


FIG. 45A

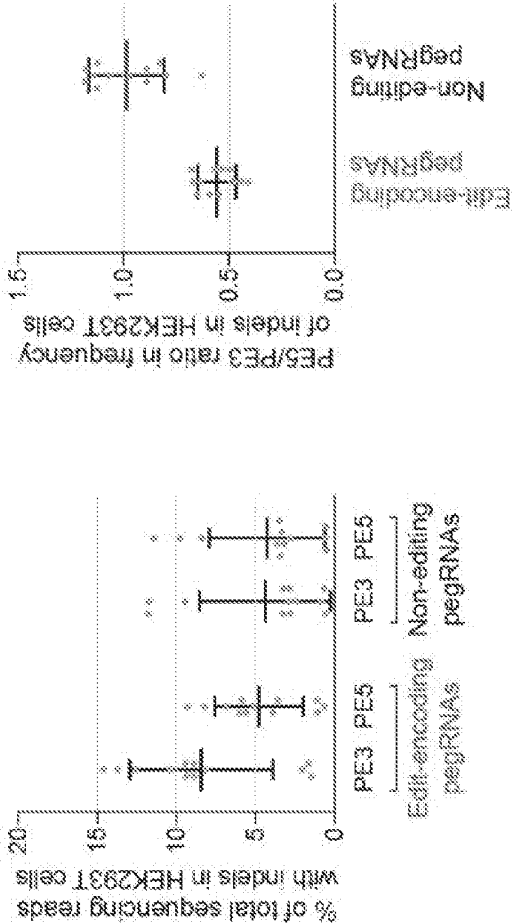


FIG. 45B

FIG. 45C

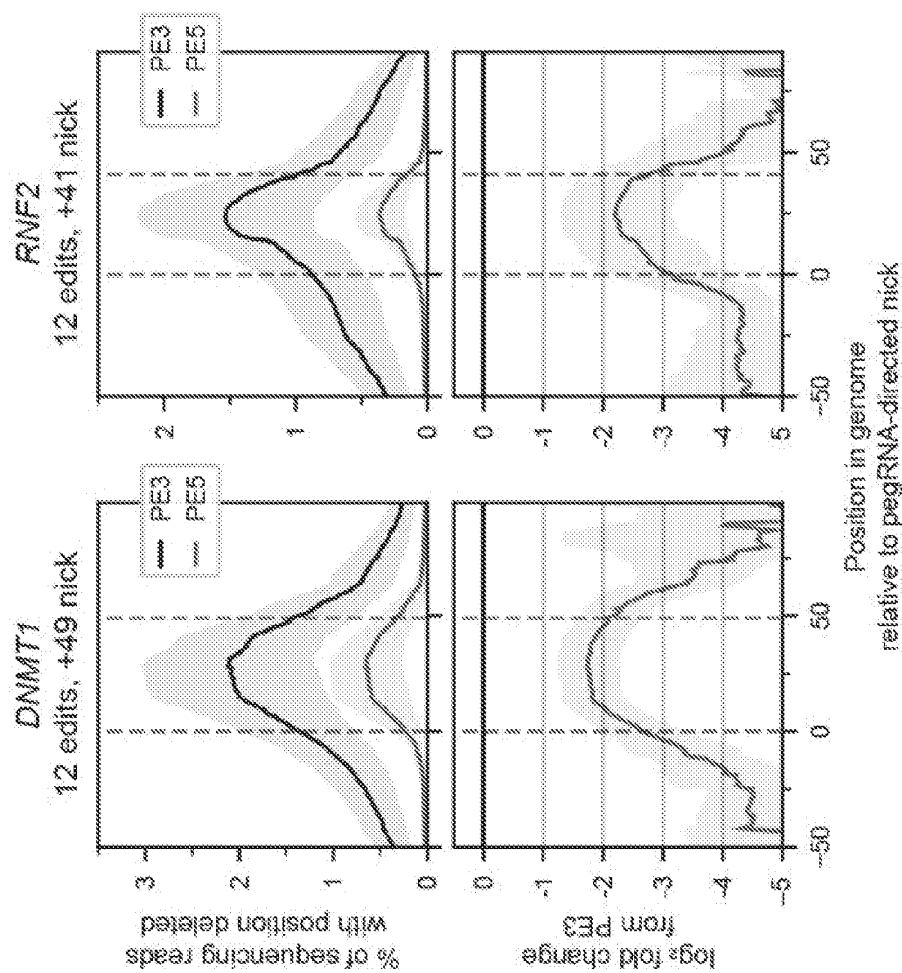


FIG. 45D

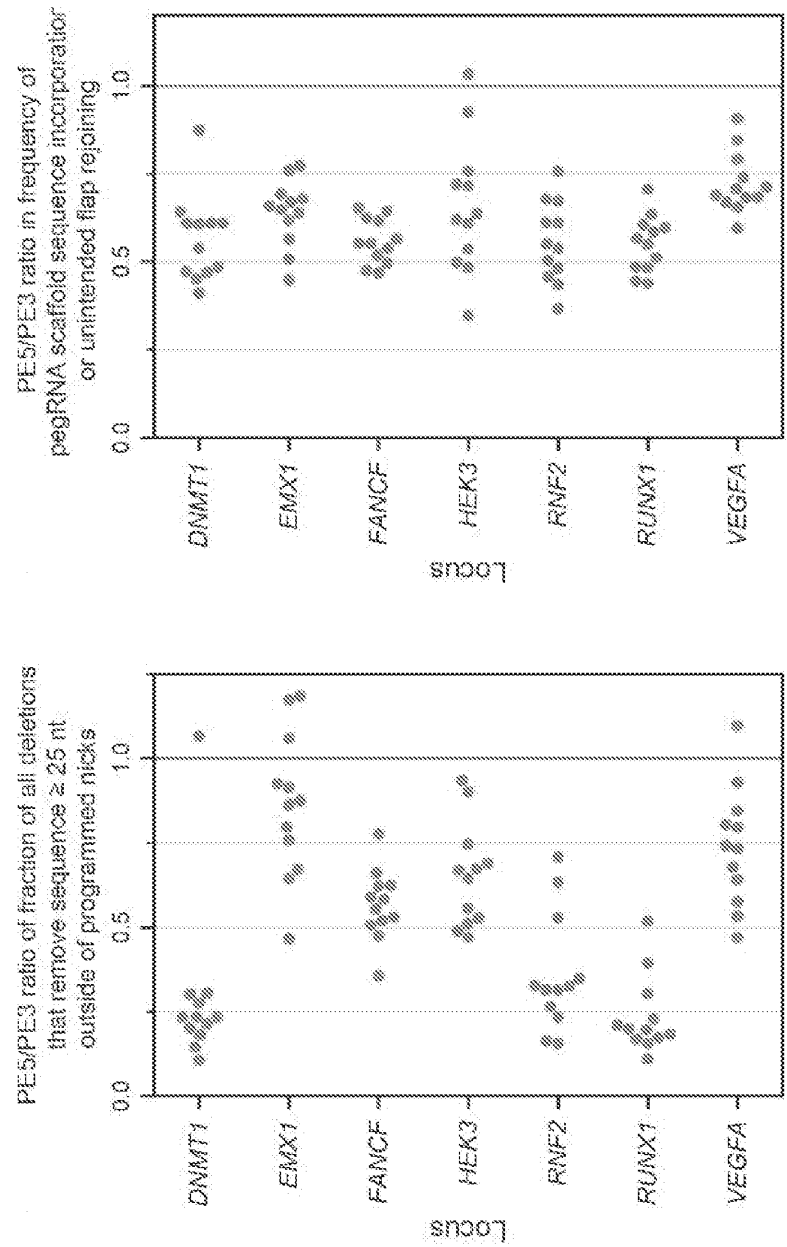


FIG. 45E

FIG. 45F

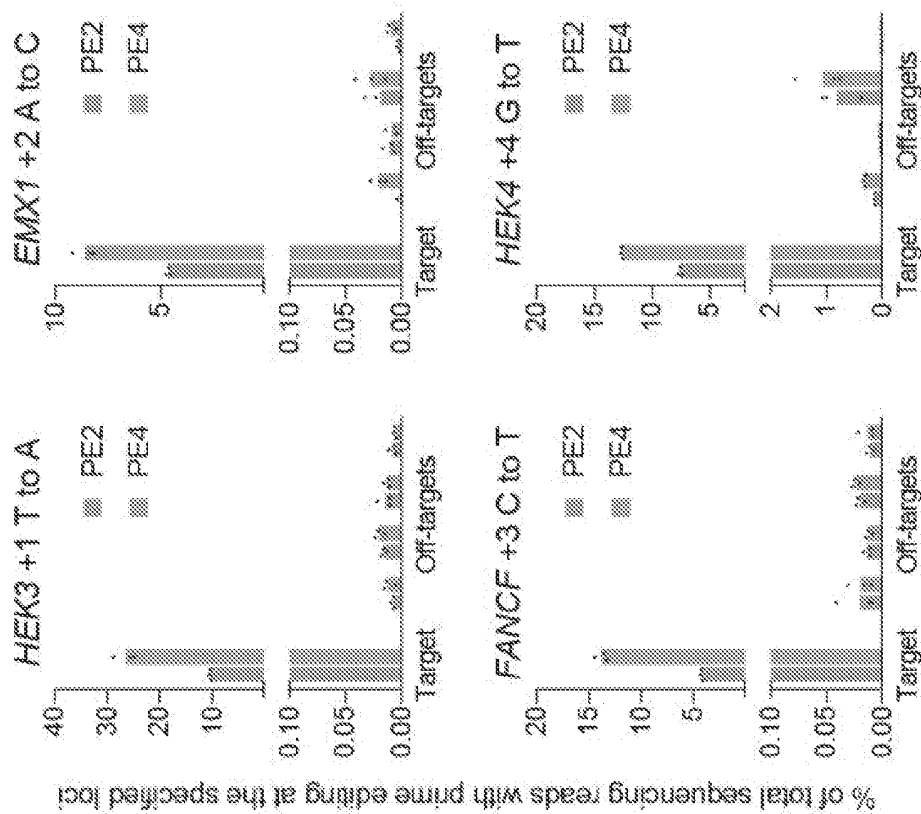


FIG. 45G

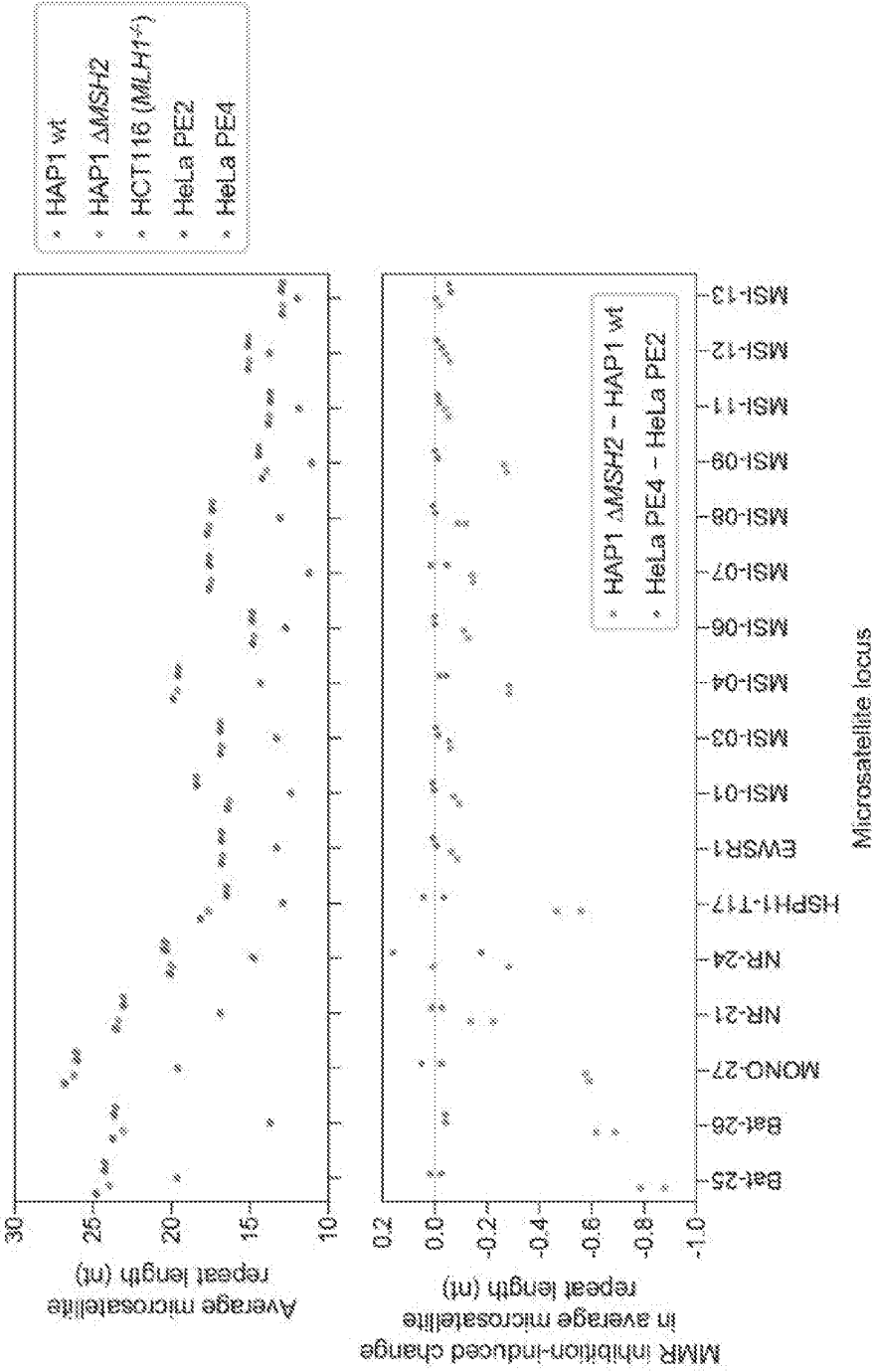


FIG. 45H

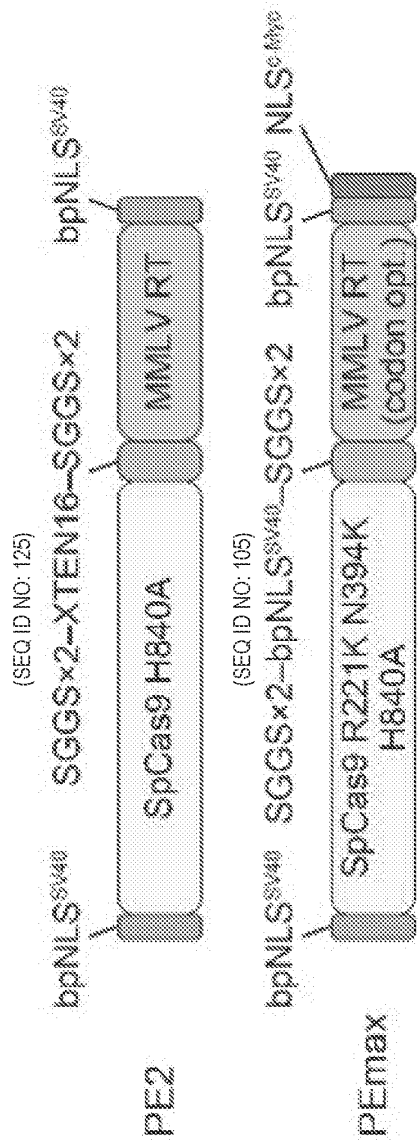


FIG. 46A

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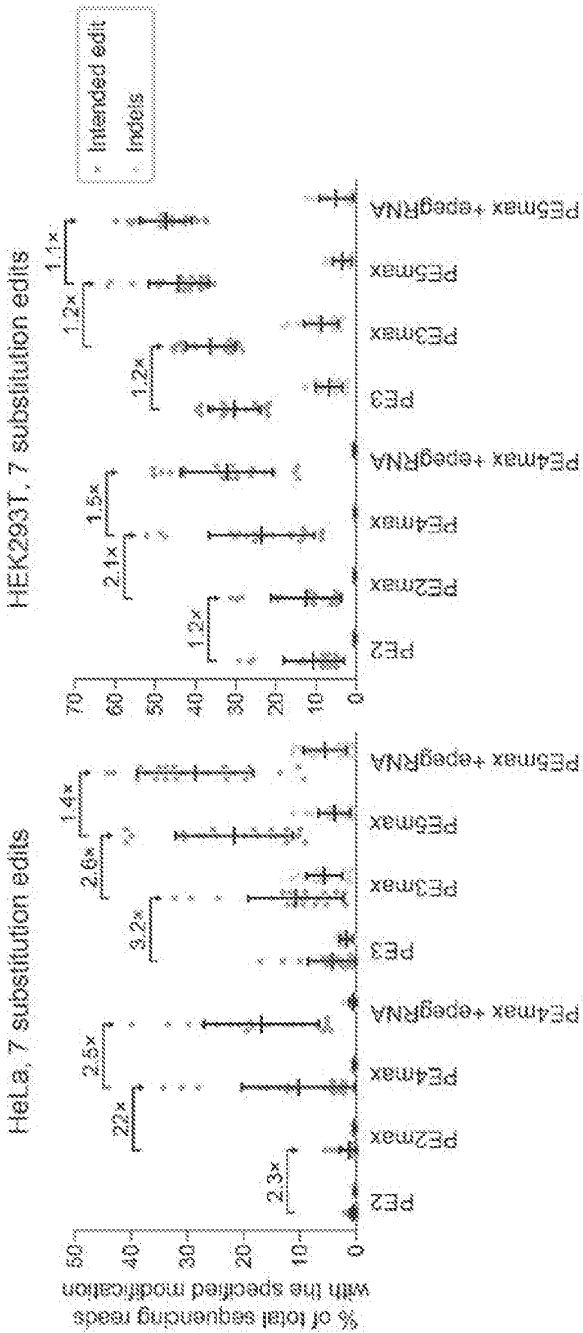


FIG. 46B

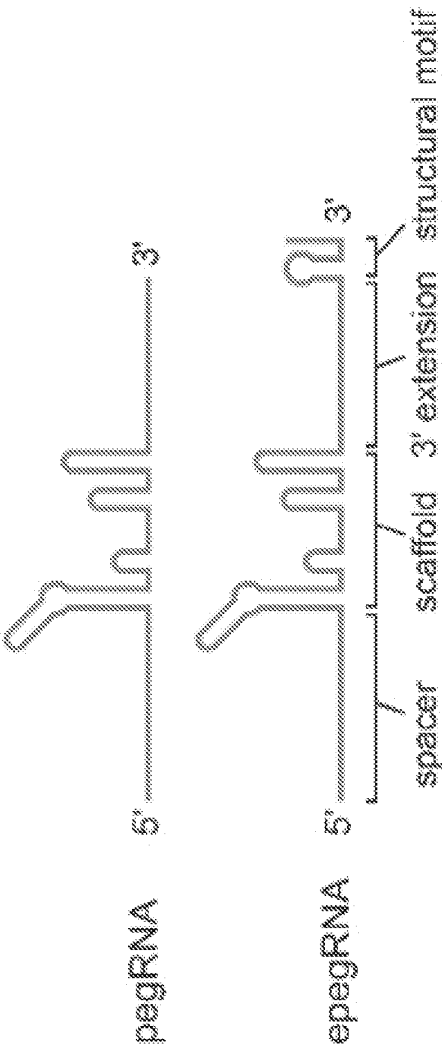


FIG. 46C

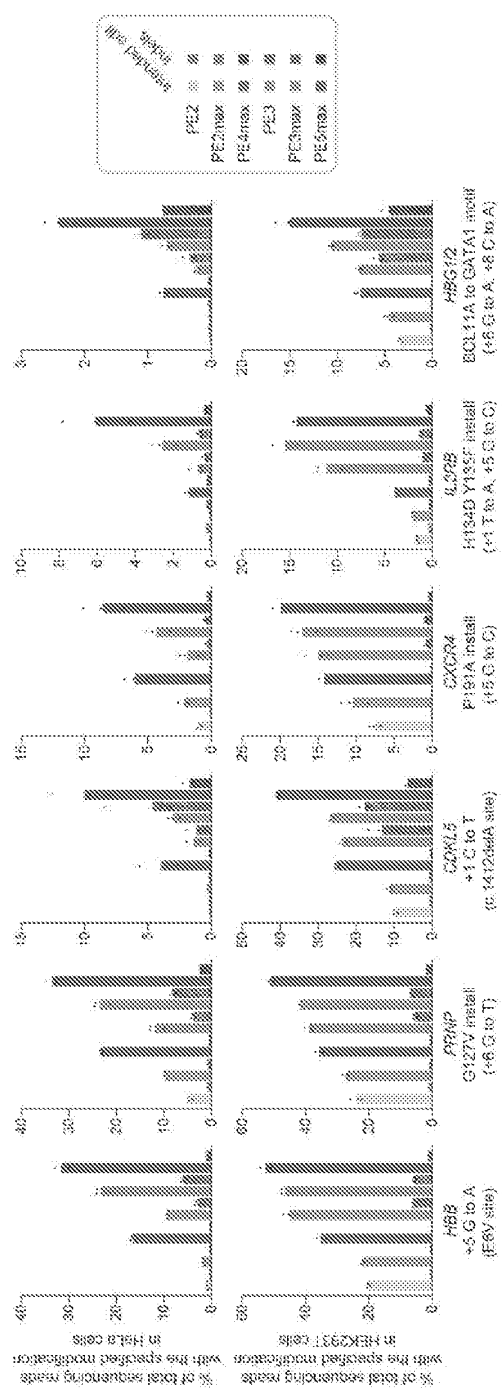


FIG. 4G

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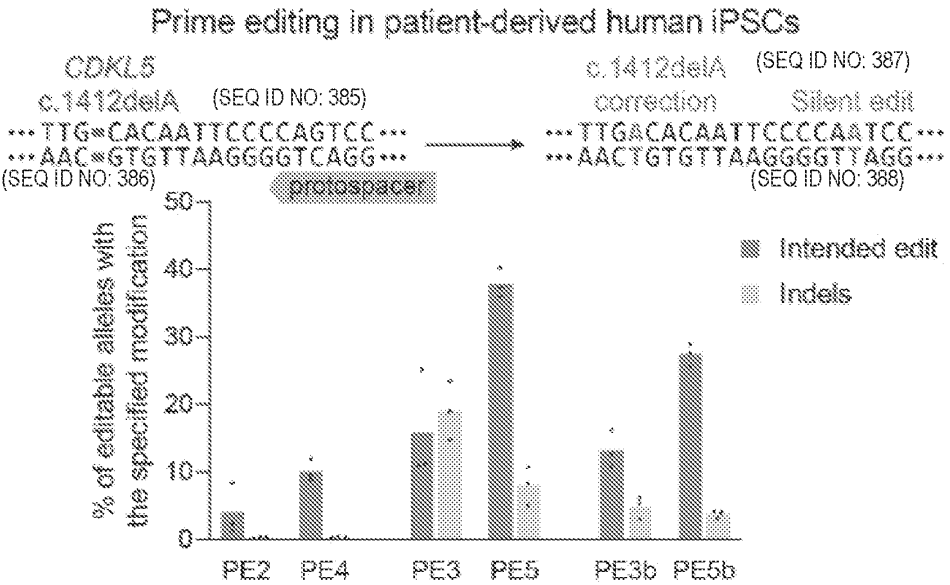


FIG. 46E

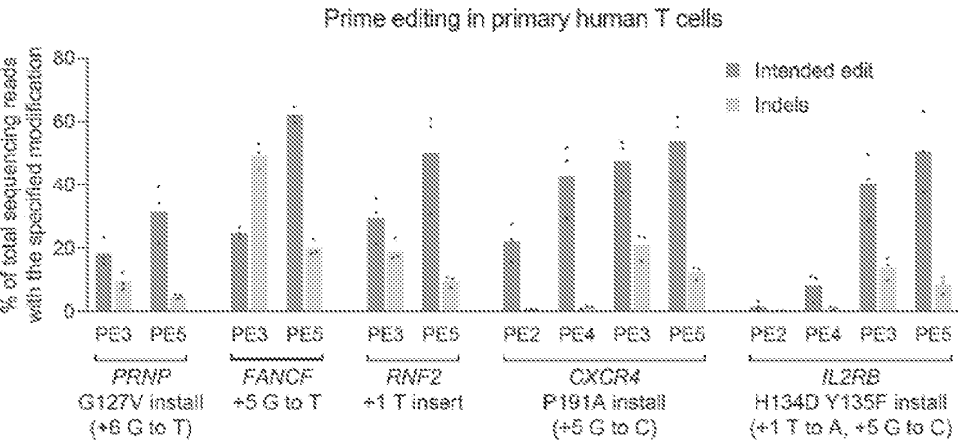


FIG. 46F

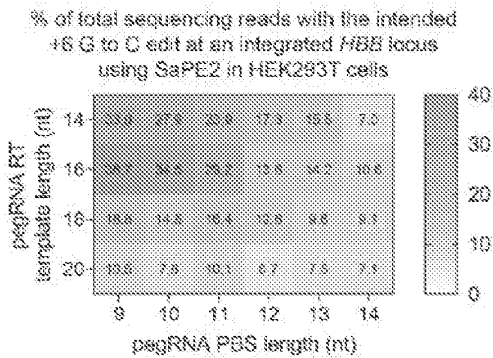


FIG. 47A

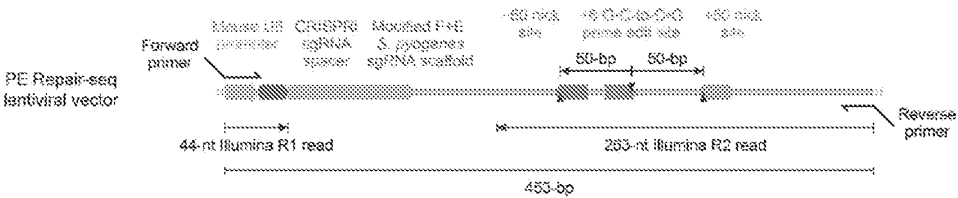


FIG. 47B

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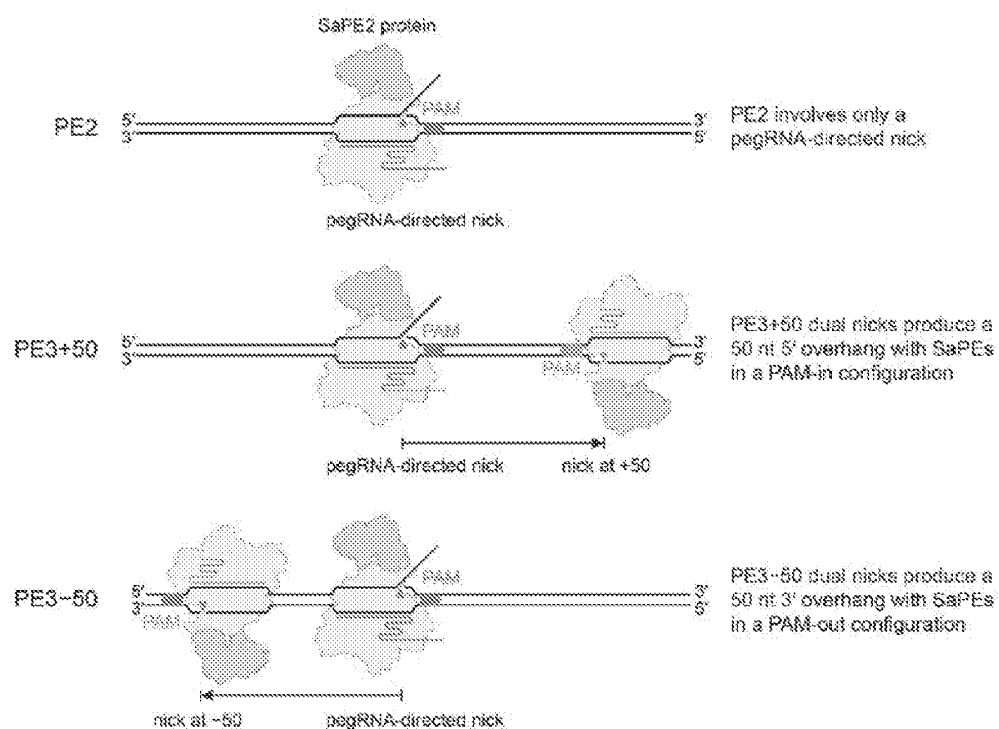


FIG. 47C

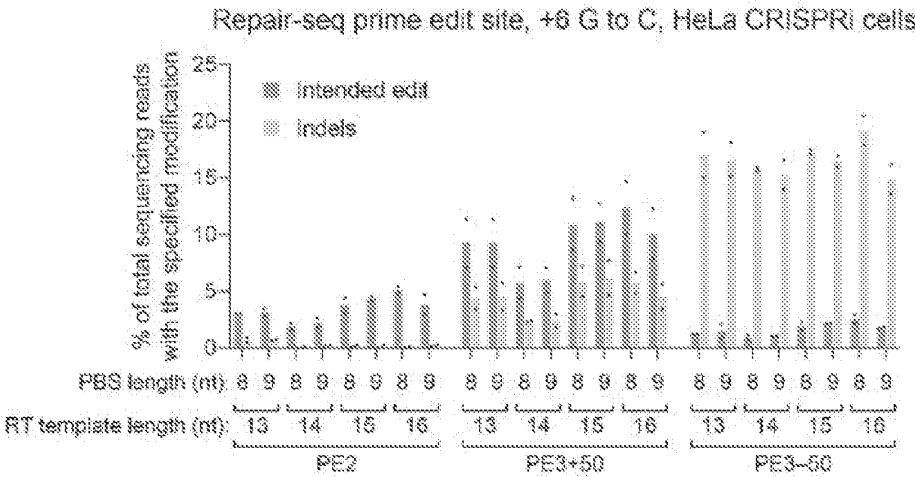


FIG. 47D

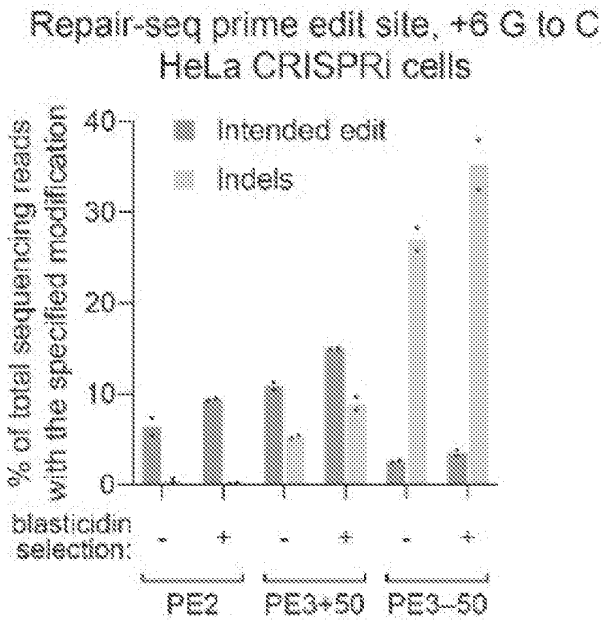


FIG. 47E

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Functional annotation class	Number of genes in CRISPRi sgRNA library
Recombinational repair	41
Double-strand break repair	36
Nucleotide-excision repair	30
Base-excision repair	23
Postreplication repair	16
Mismatch repair	16
DNA repair (other)	50
Cellular response to stimulus	4
Nuclear division	12
Cell cycle checkpoint	12
mRNA processing	21
DNA replication	23
Protein modification	24
Other	39
Regulation of transcription	46
Chromatin processes	83
Total	476

FIG. 47F

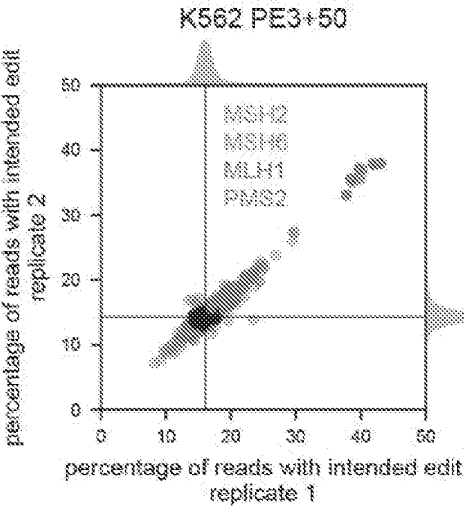


FIG. 47G

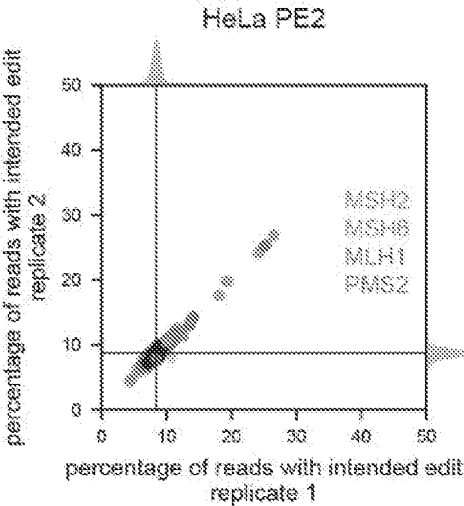


FIG. 47H

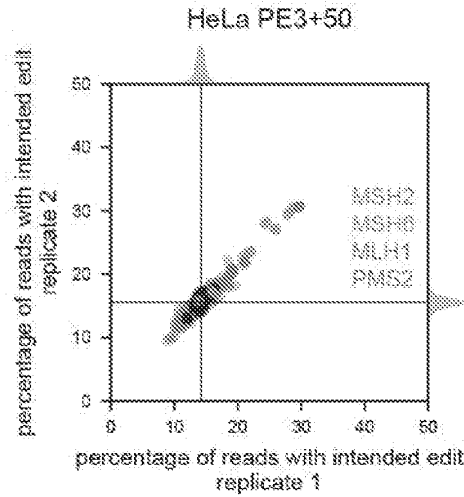


FIG. 47I

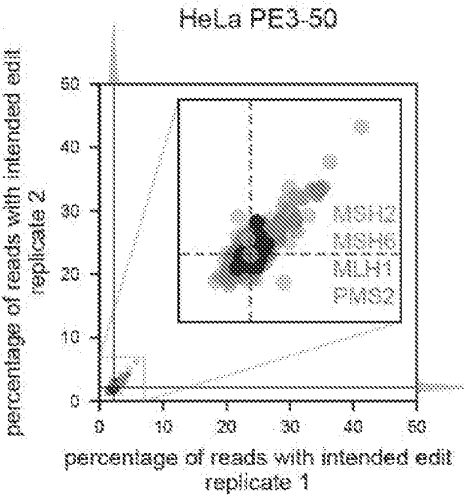


FIG. 47J

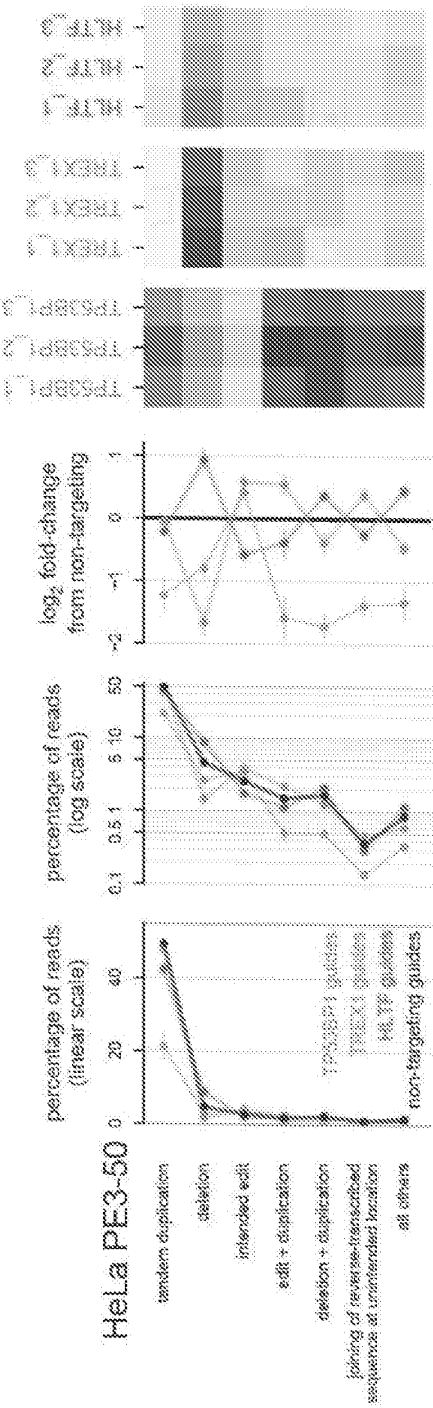


FIG. 48A

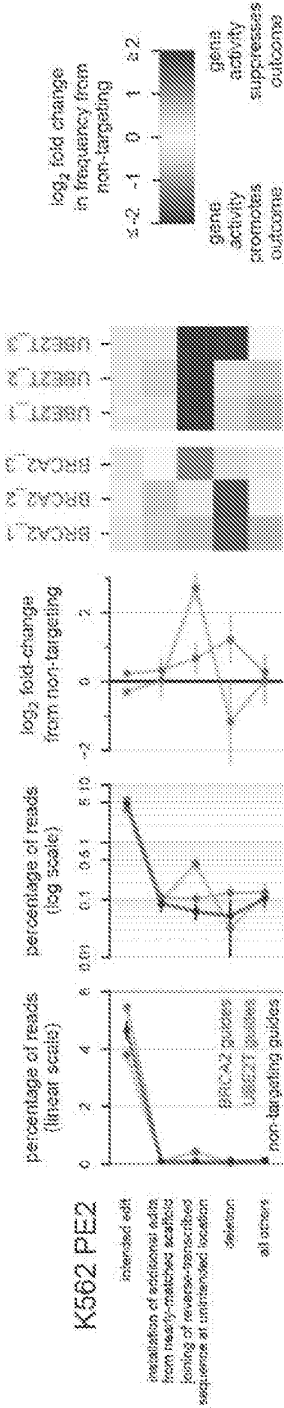


FIG. 48B

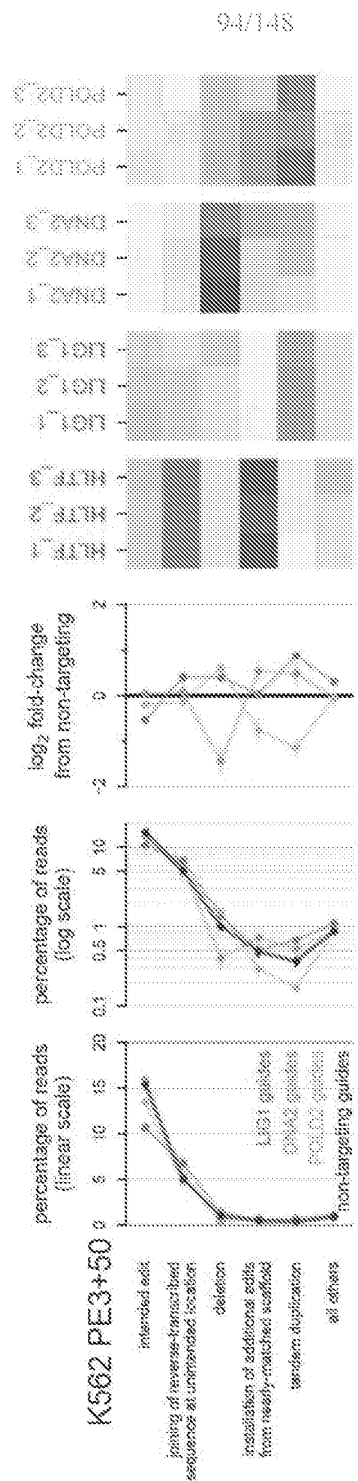
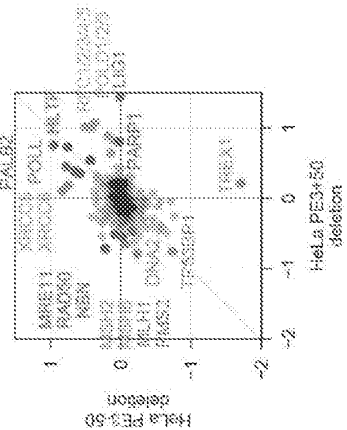
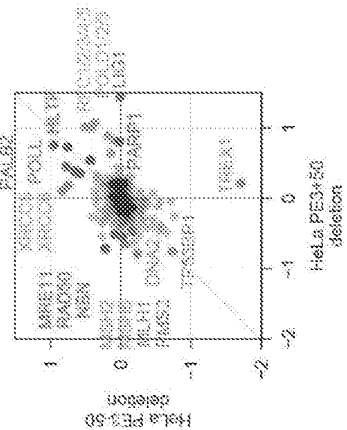
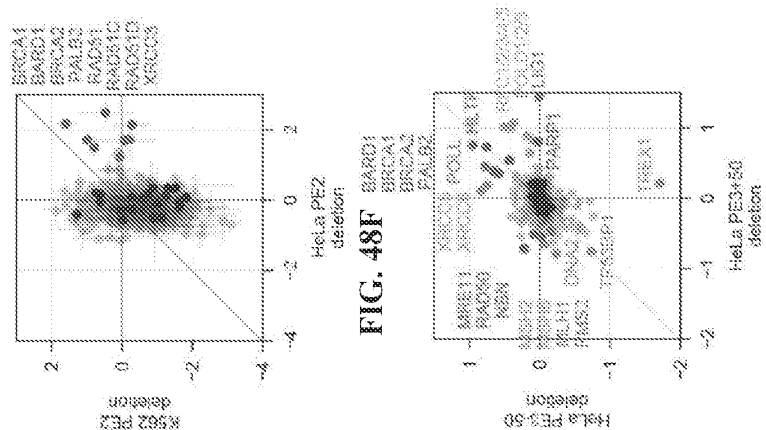
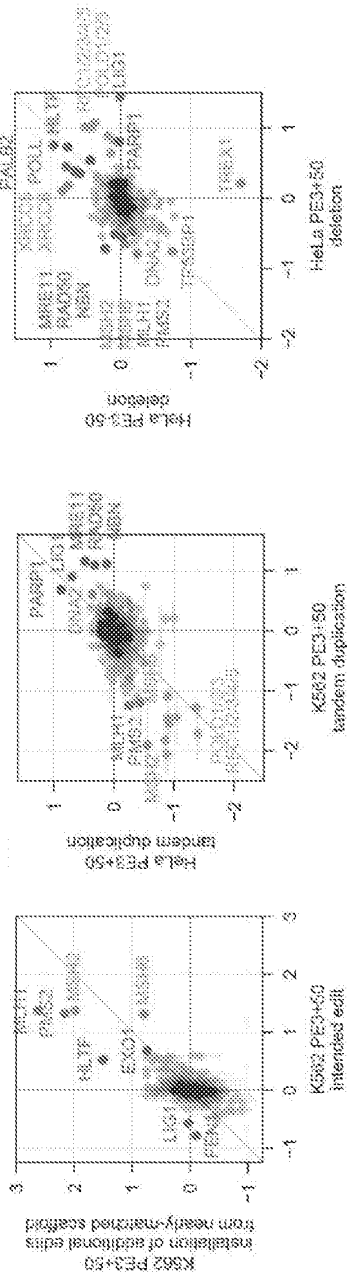
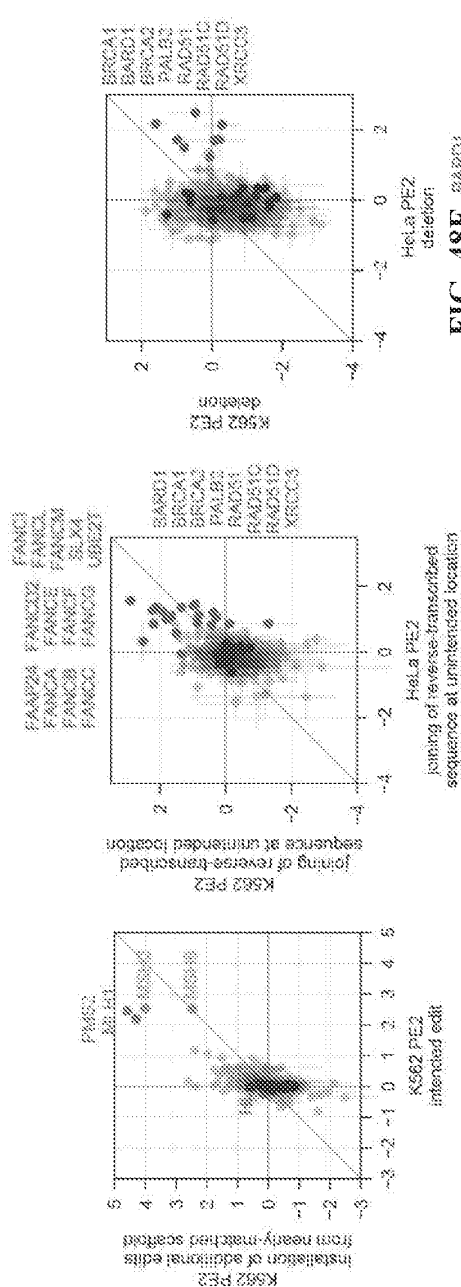


FIG. 48C



log, fold change in frequency of indicated category

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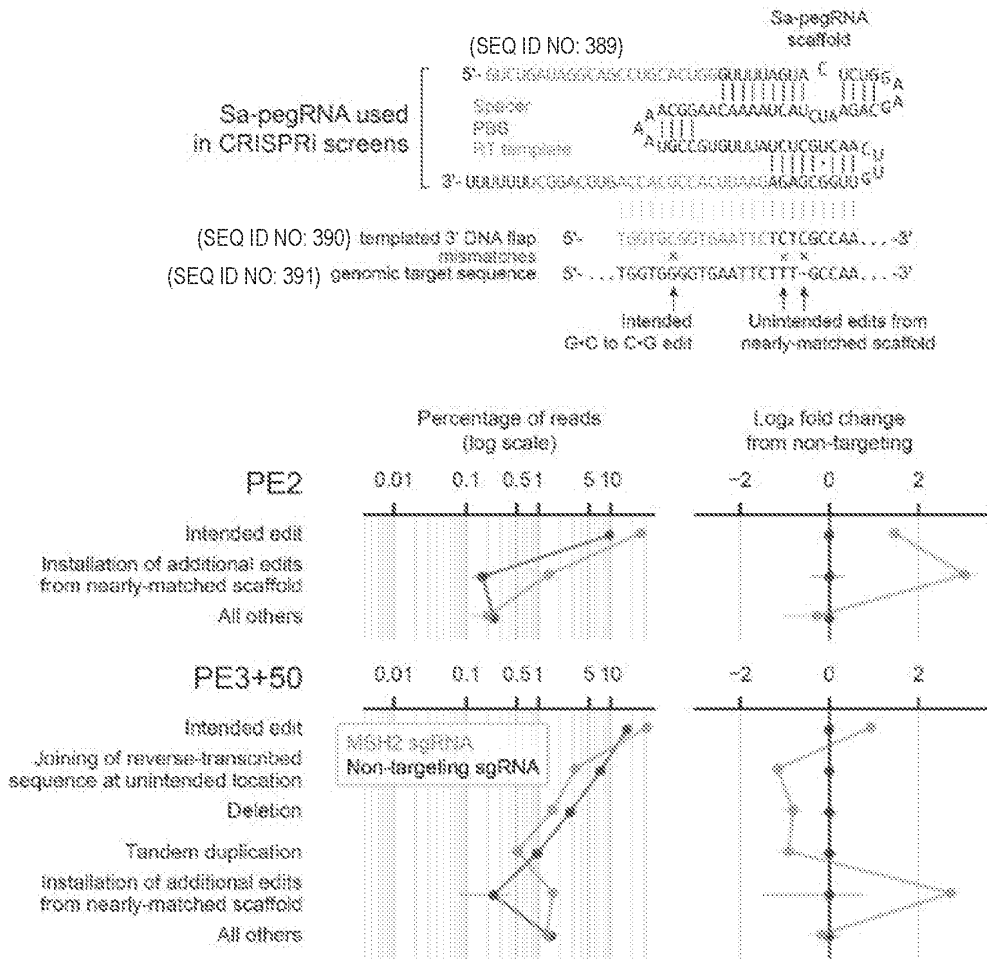


FIG. 49A

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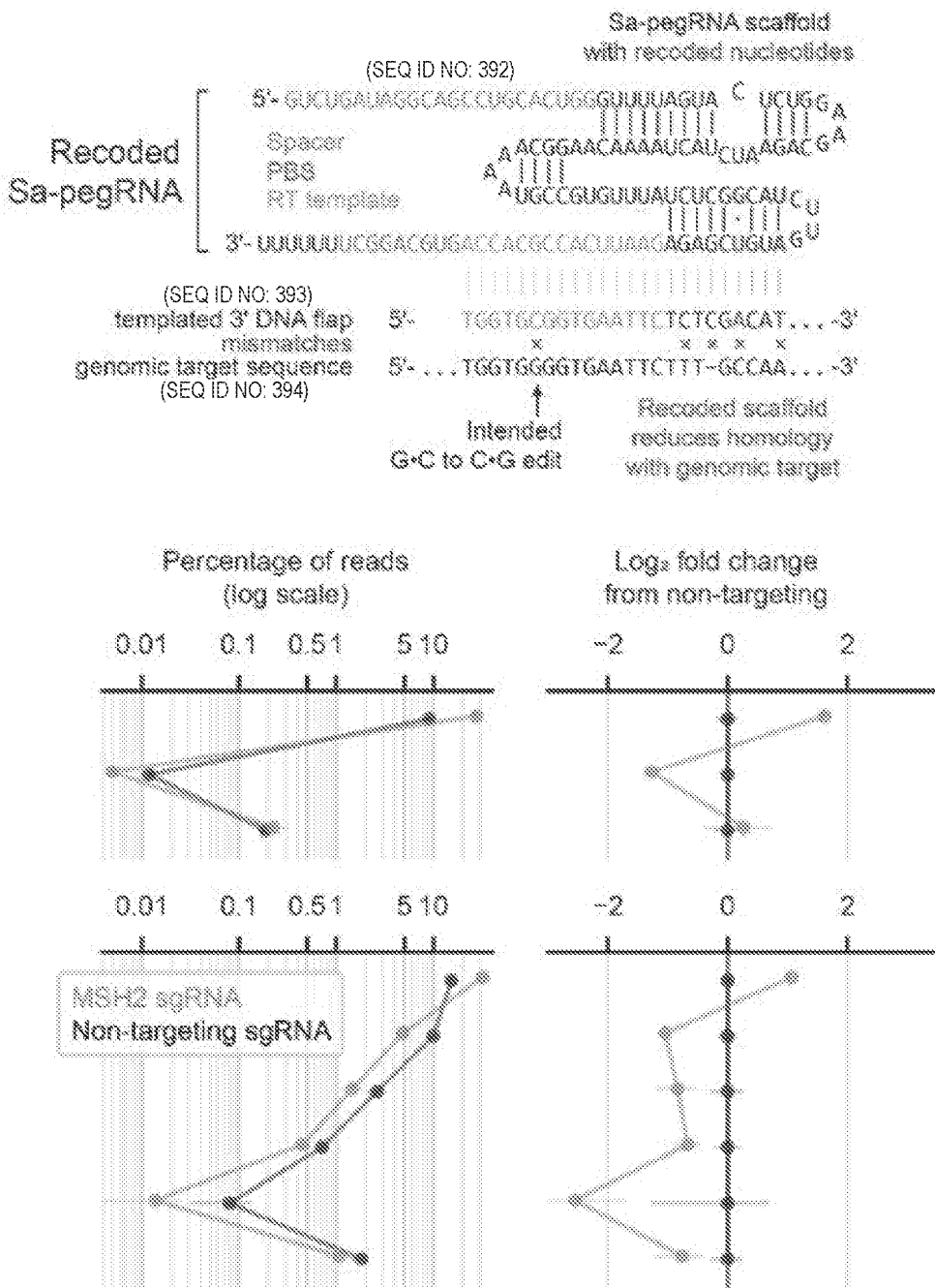


FIG. 49B

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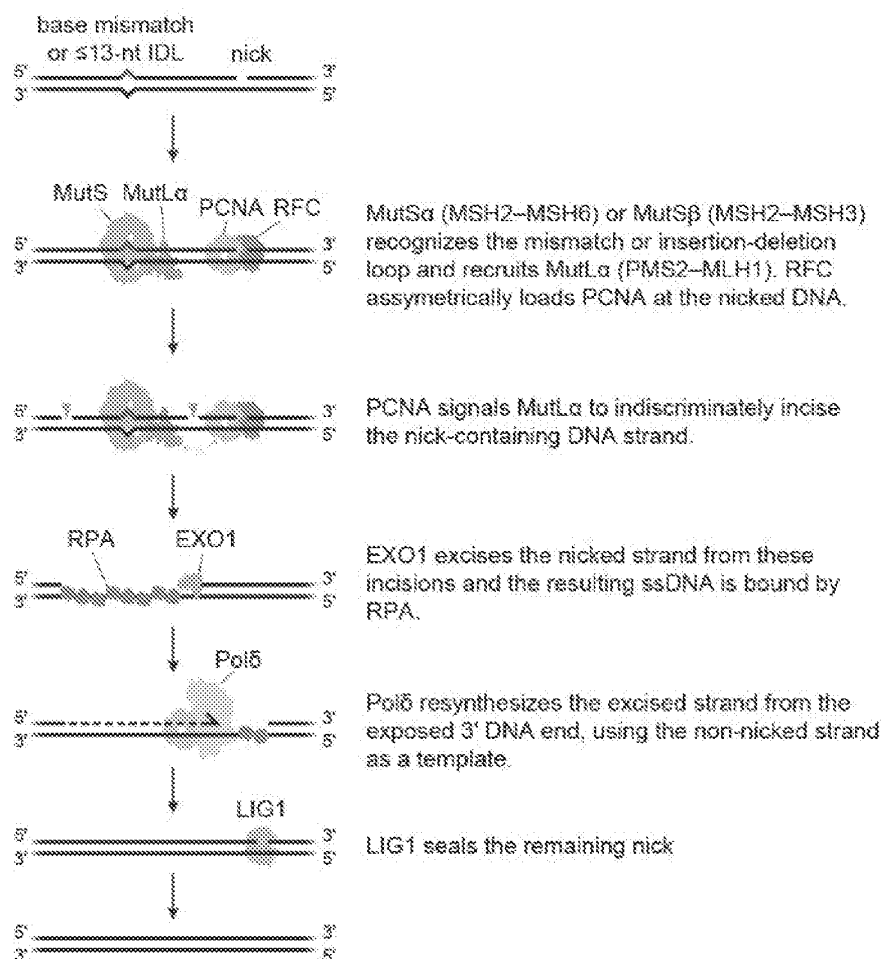
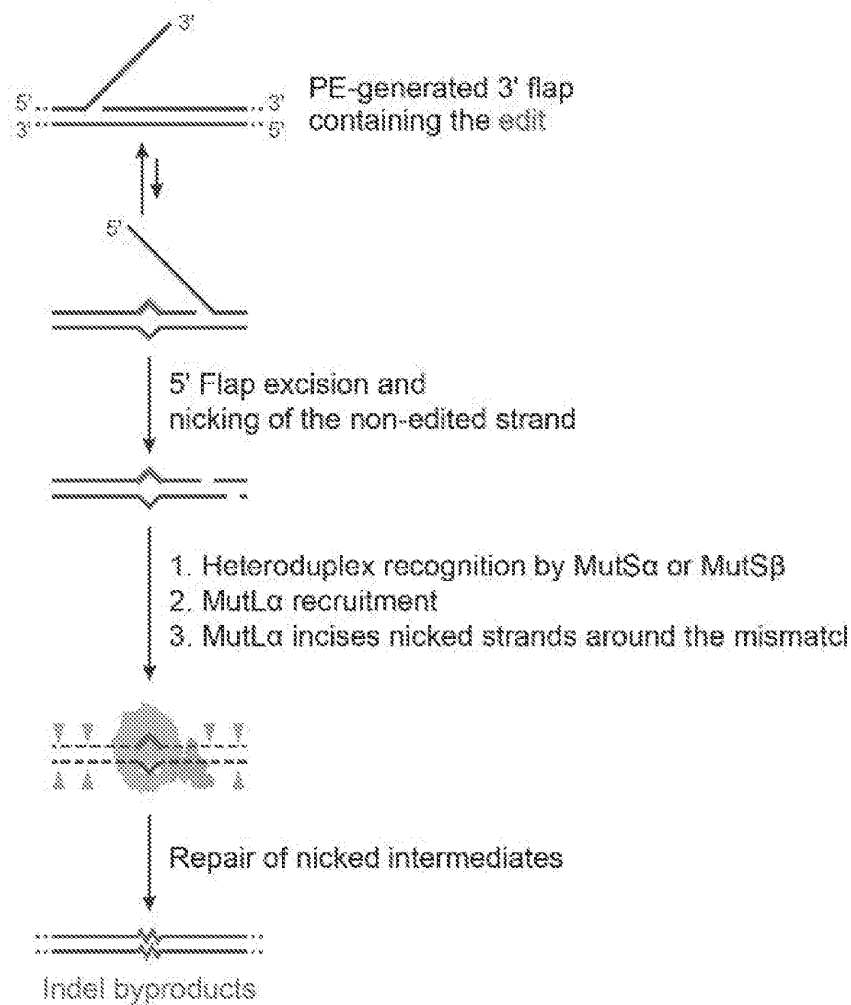


FIG. 49C

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Indel outcomes from PE3 editing system

**FIG. 49D**

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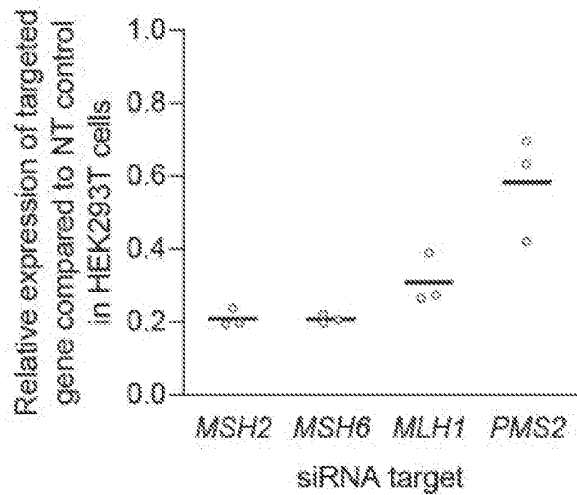


FIG. 49E

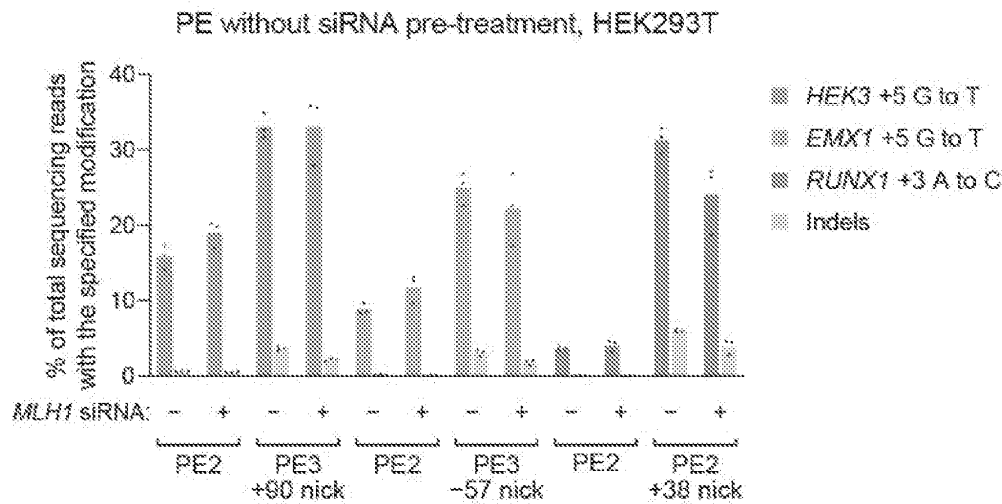
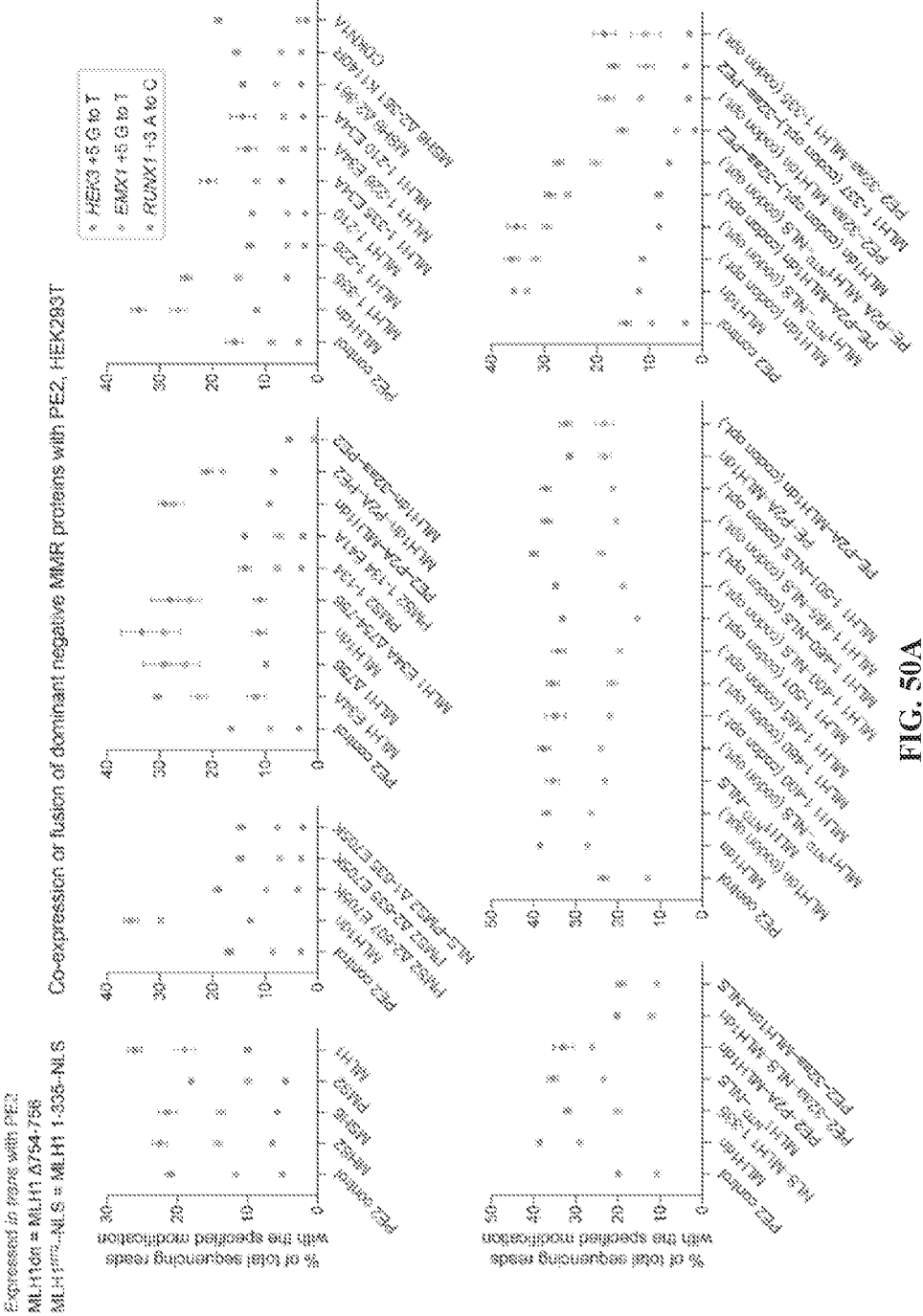


FIG. 49F



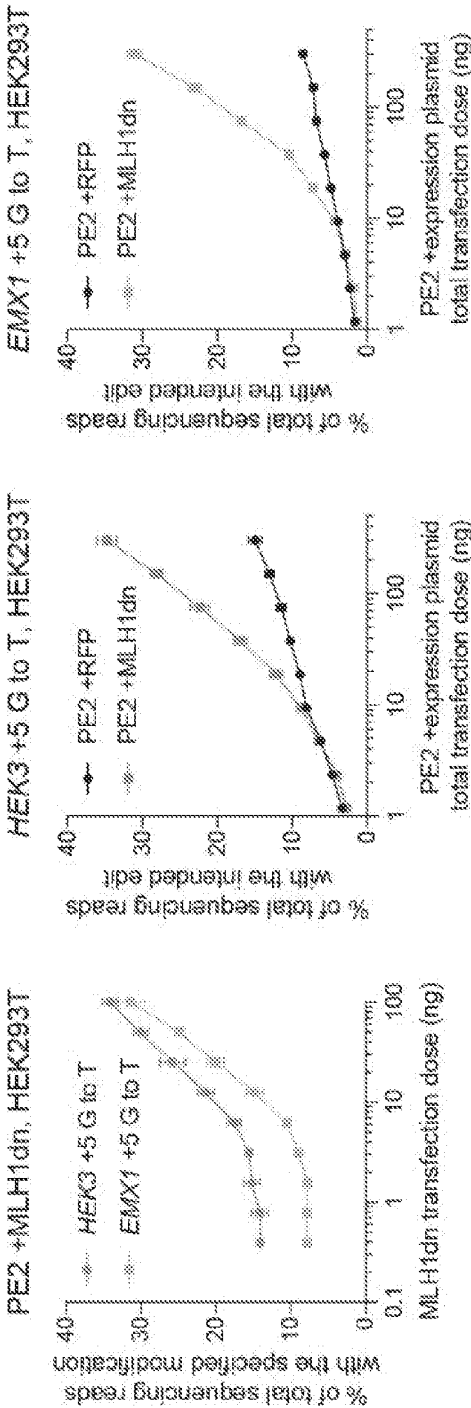


FIG. 50B

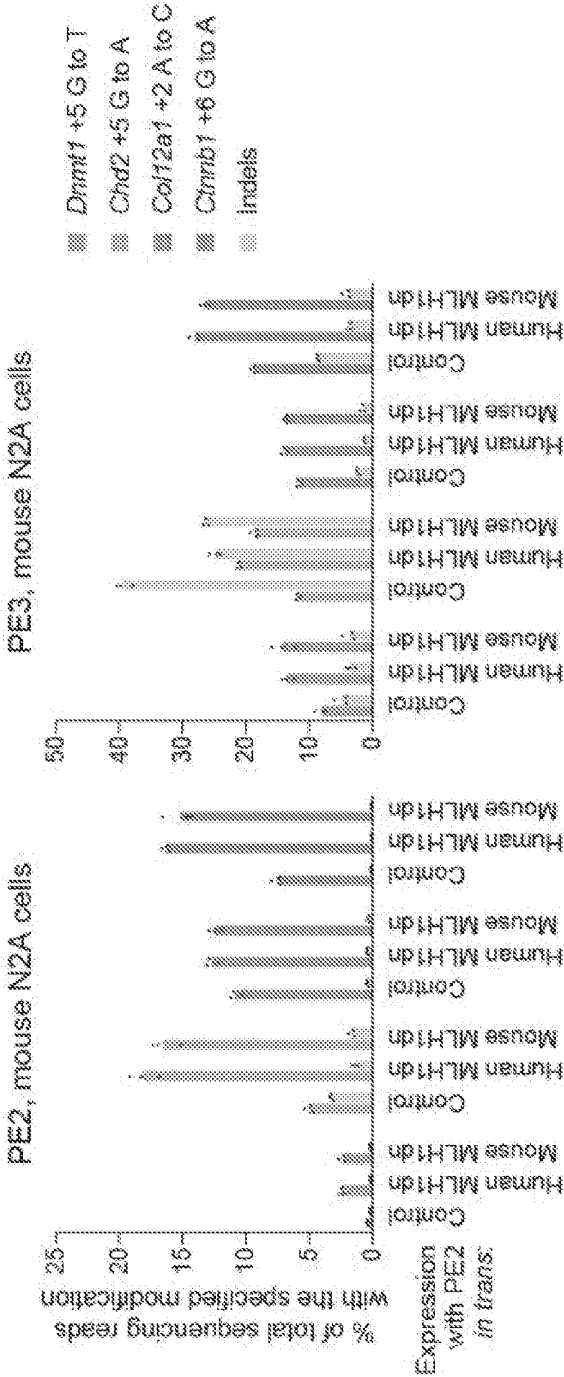


FIG. 50E

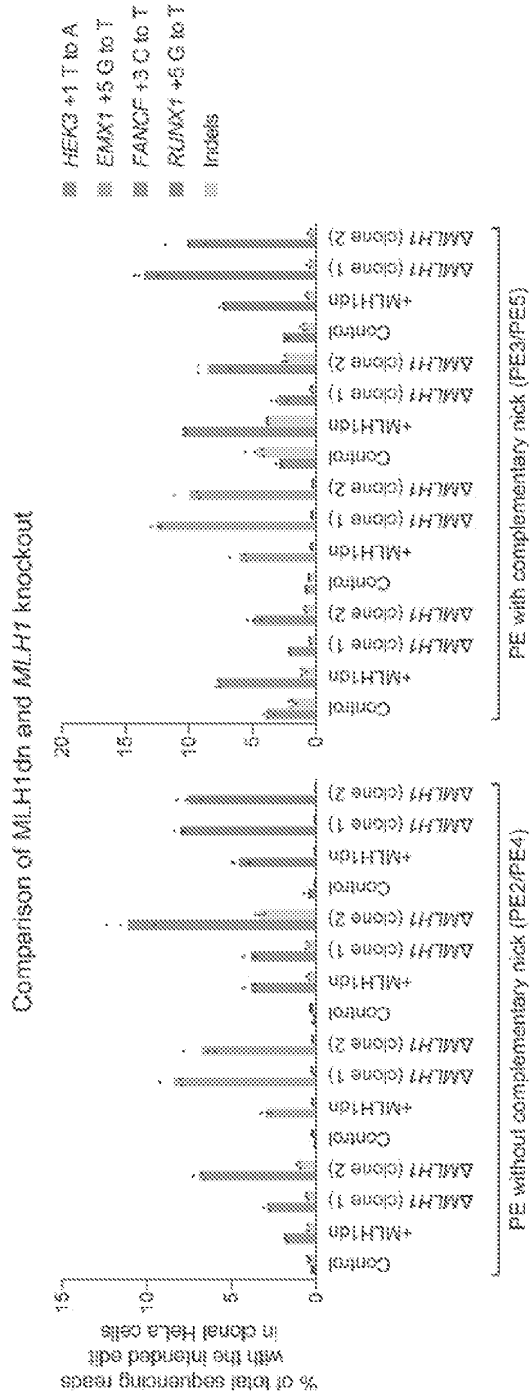


FIG. 50F

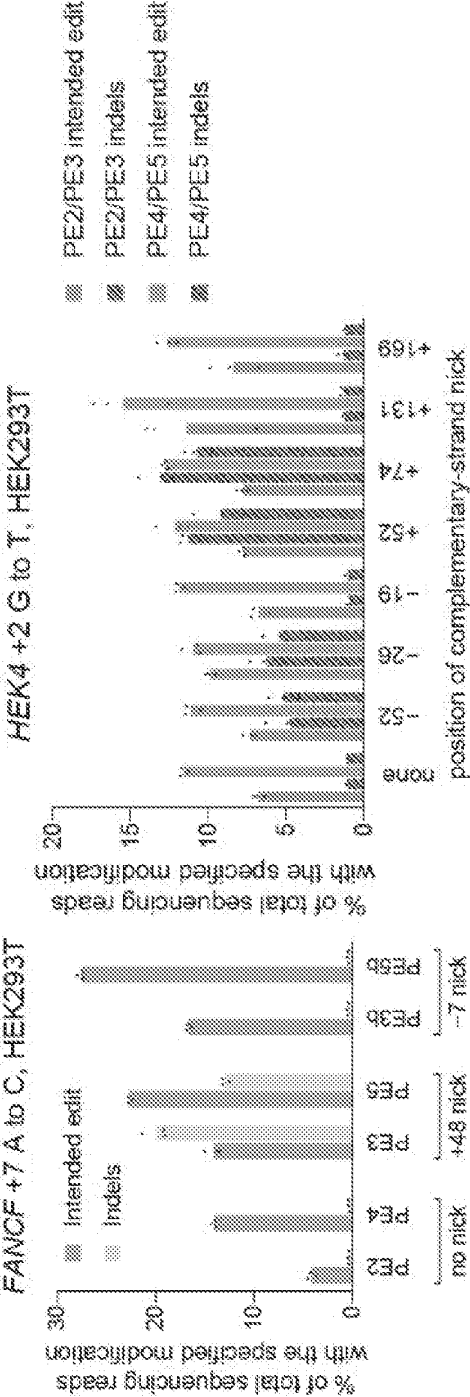


FIG. 50G

FIG. 50H

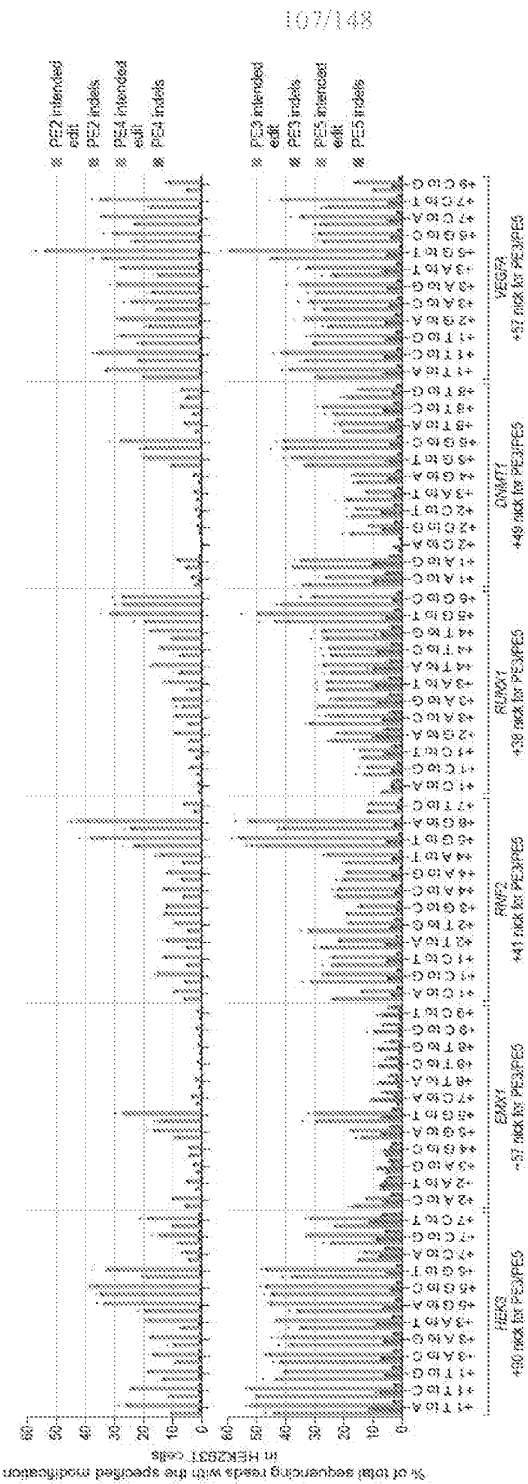
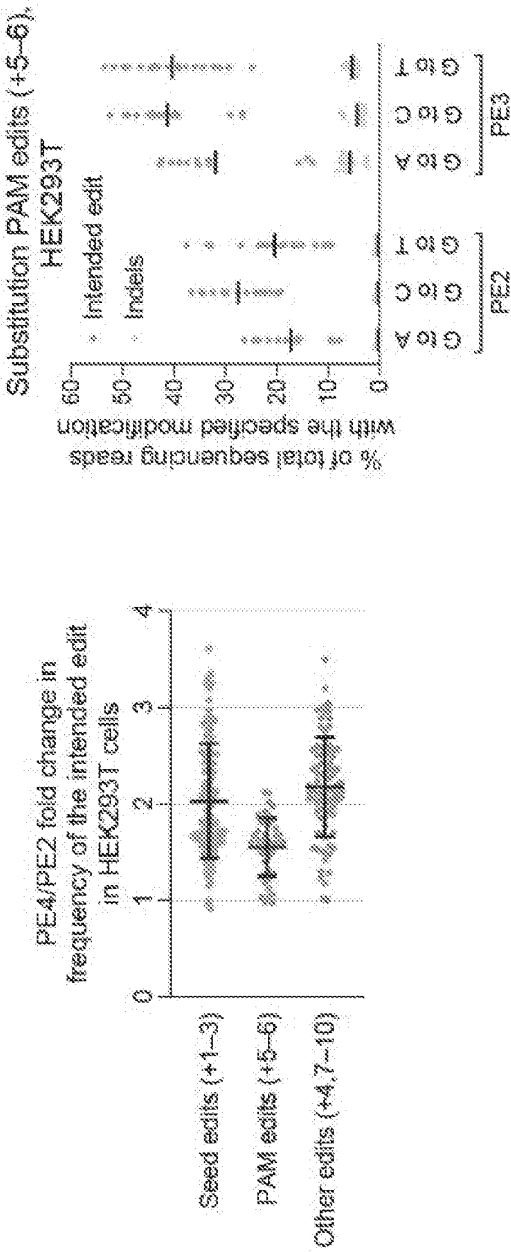


FIG. 51A



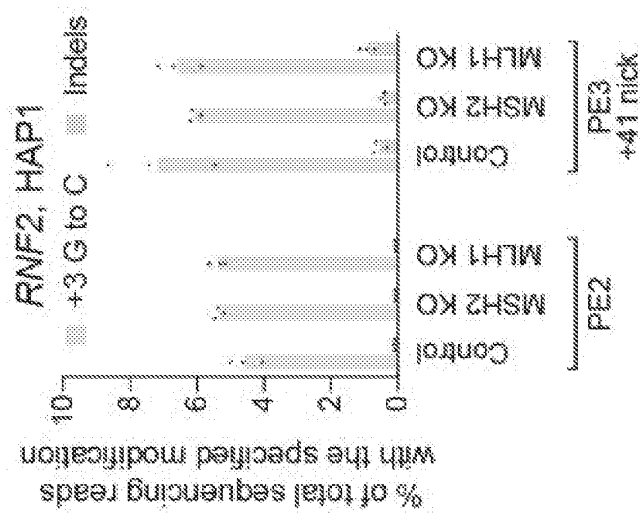


FIG. 51E

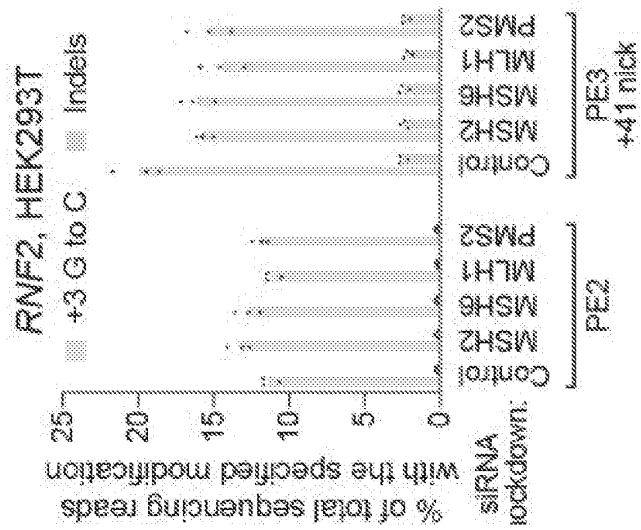


FIG. 51D

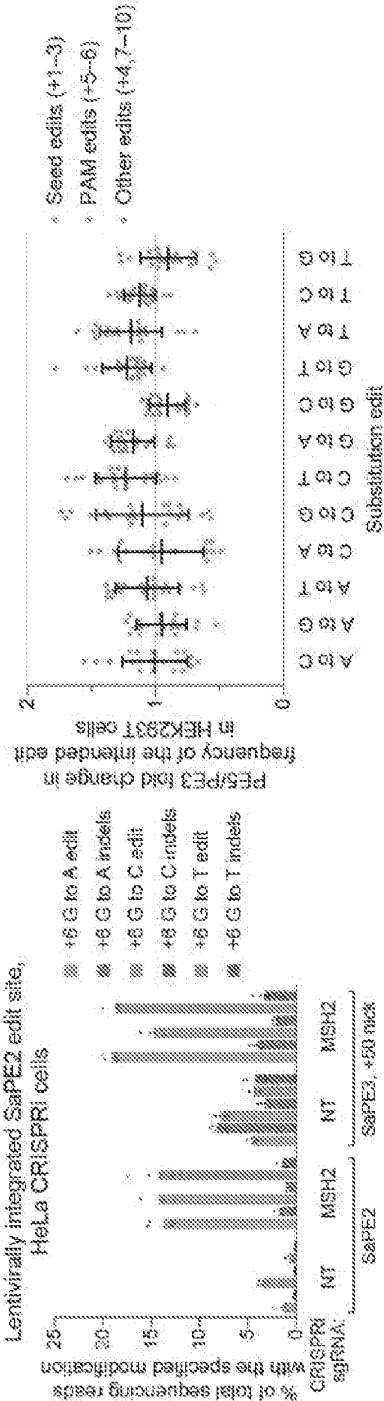


FIG. 5IF

FIG. 5IG

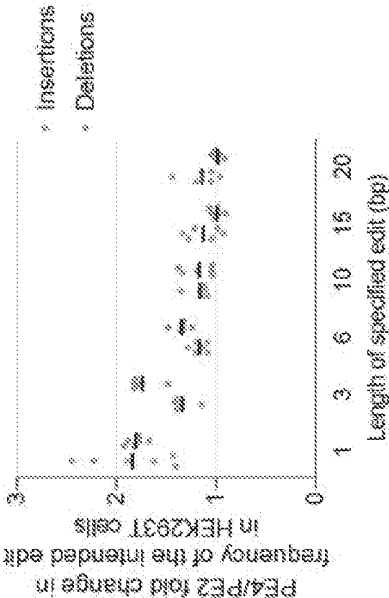


FIG. 5IH

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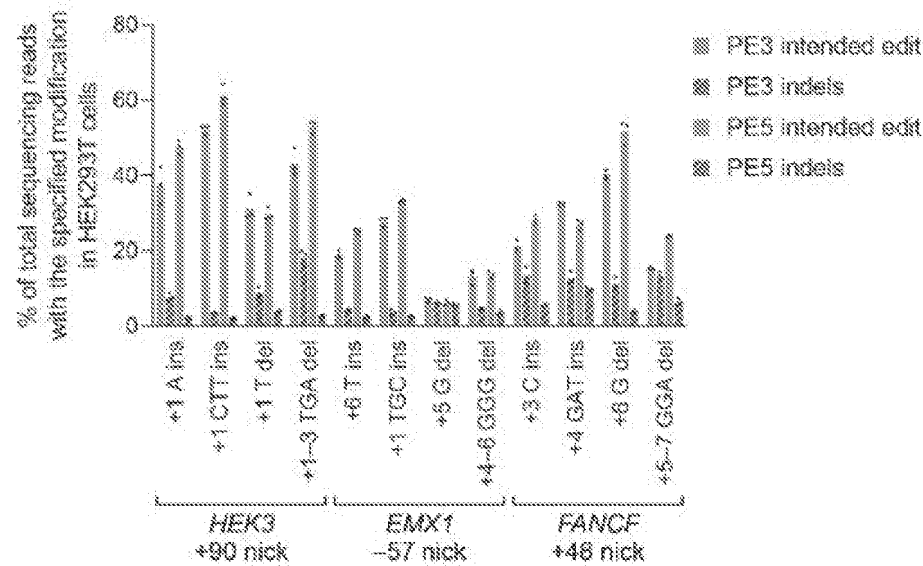


FIG. 51I

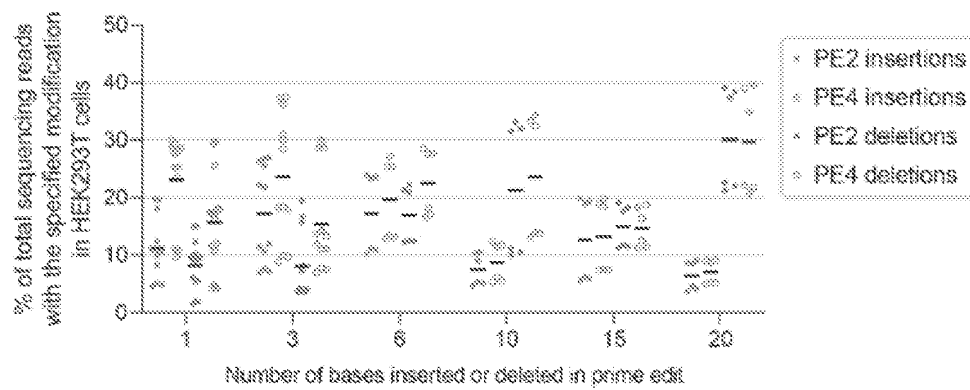


FIG. 51J

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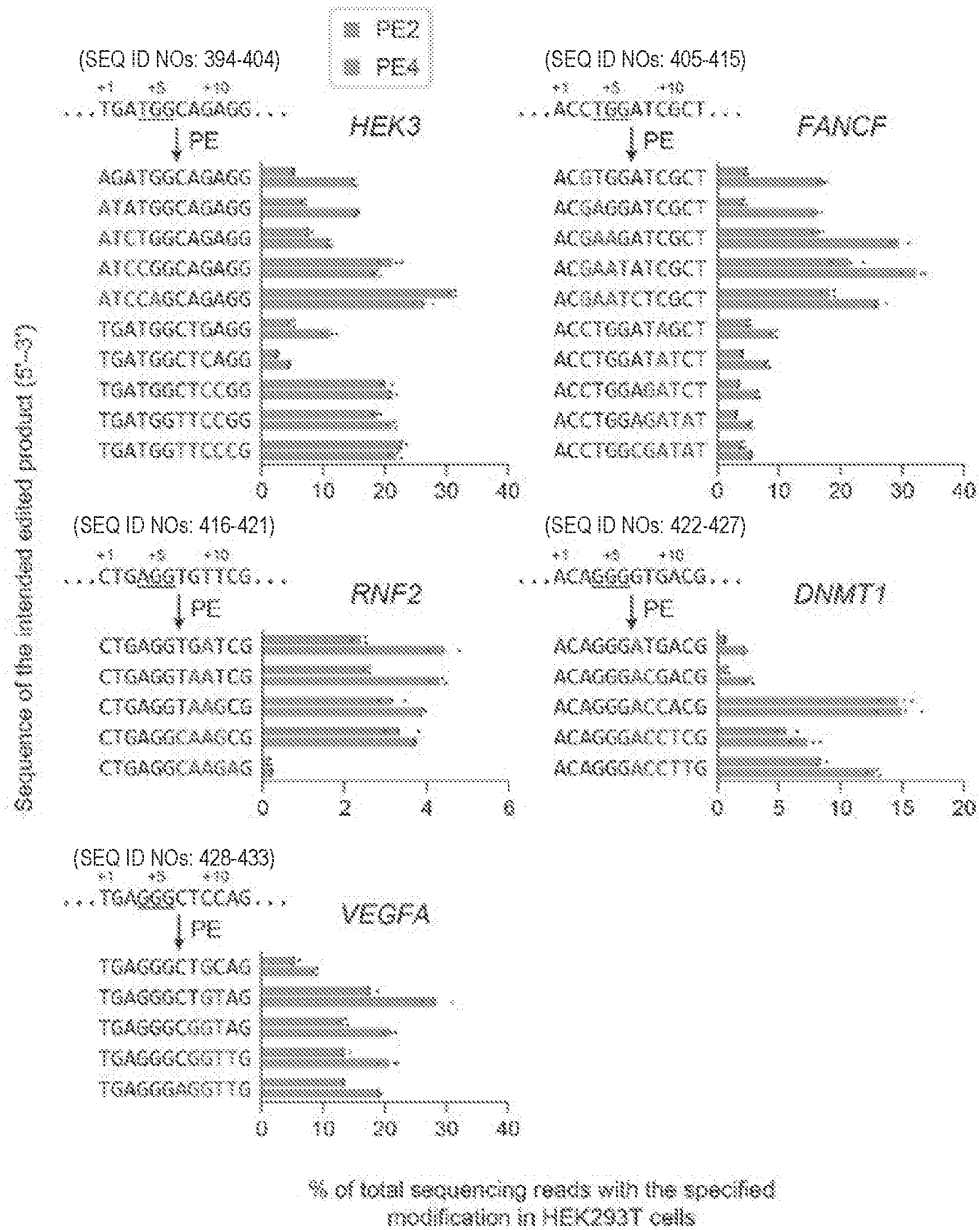


FIG. 52A

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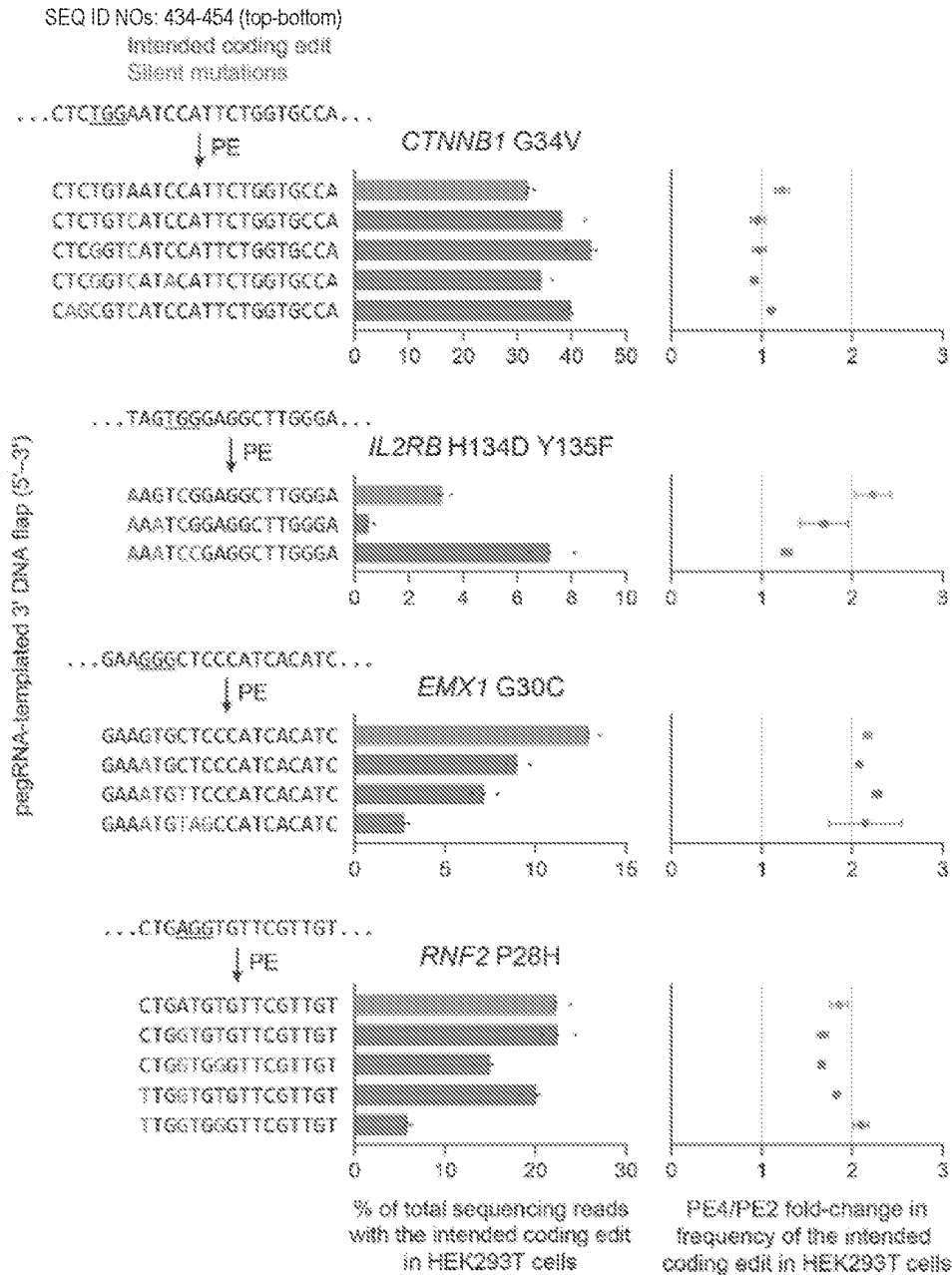


FIG. 52B

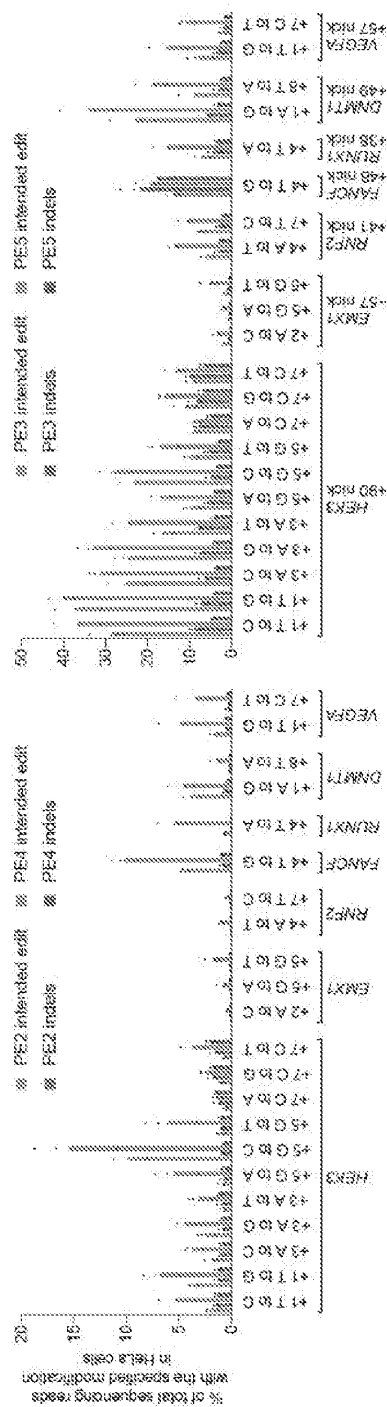


FIG. 52C

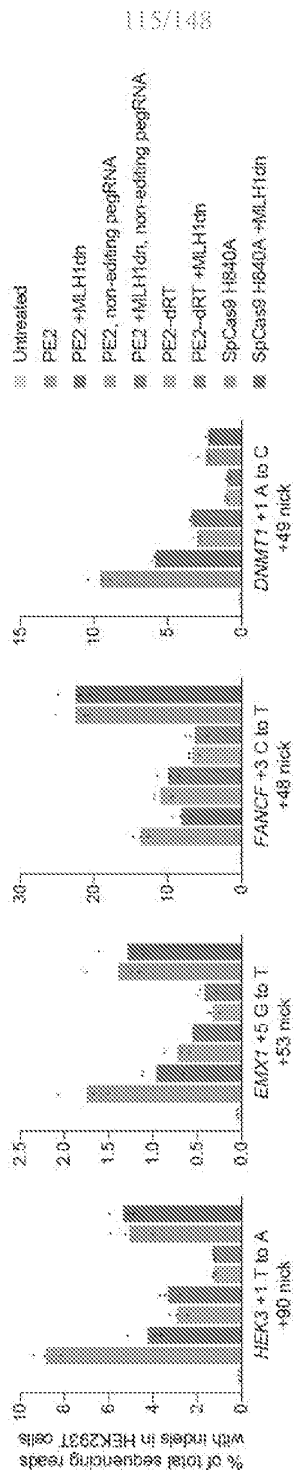


FIG. 53A

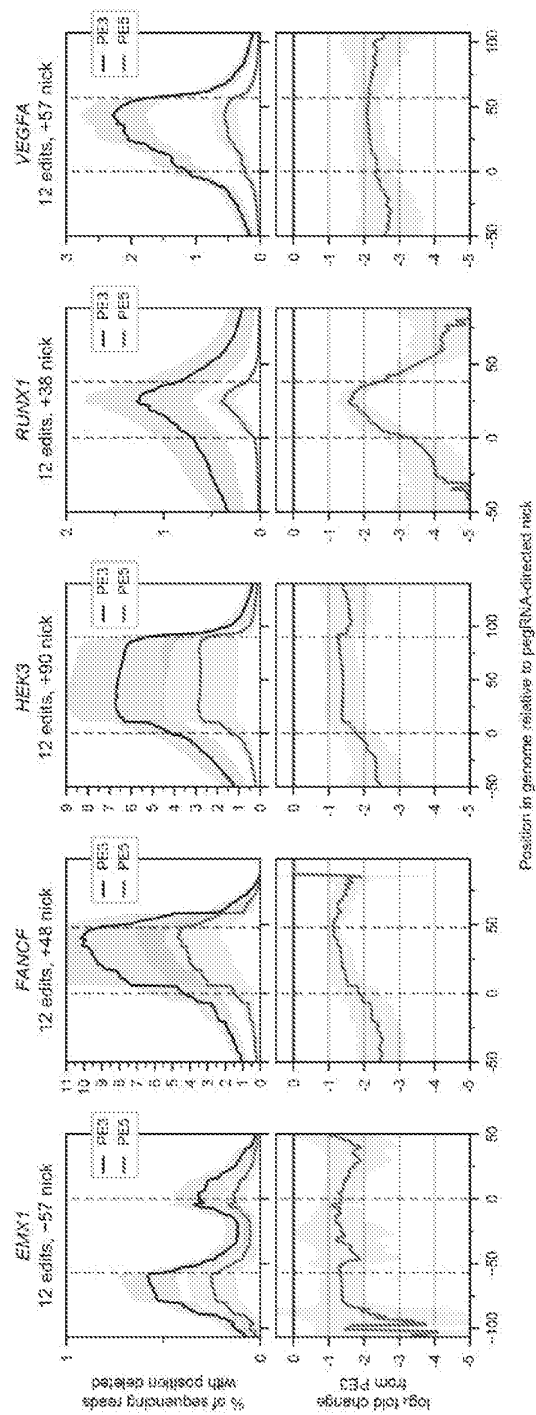


FIG. 53B

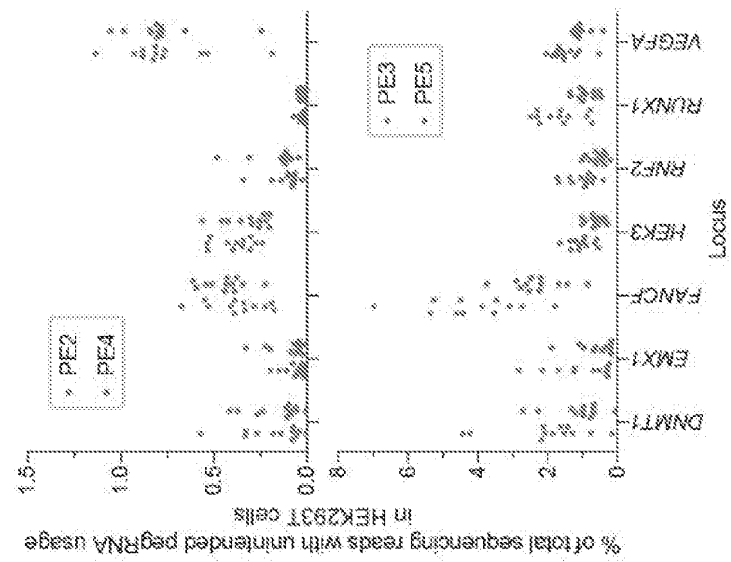


FIG. 53D

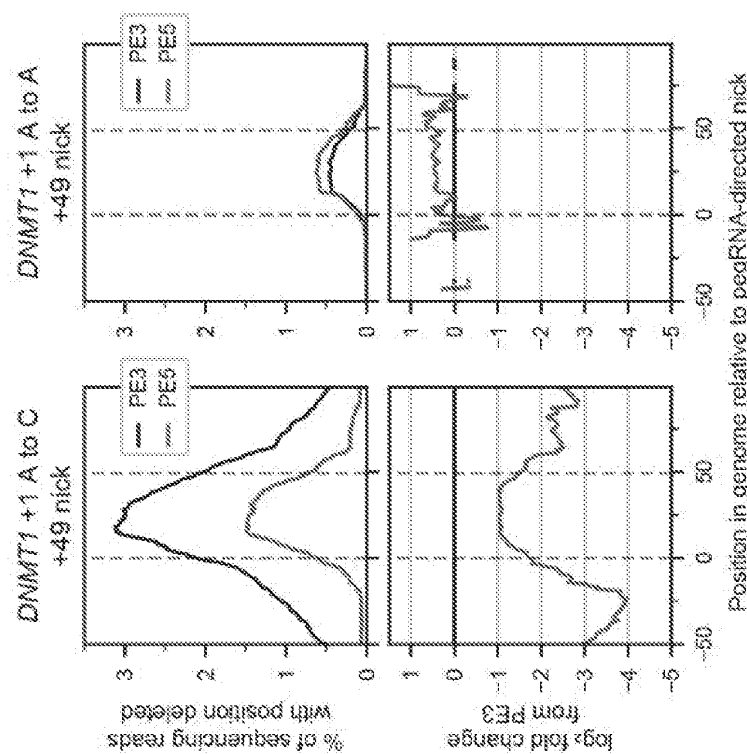


FIG. 53C

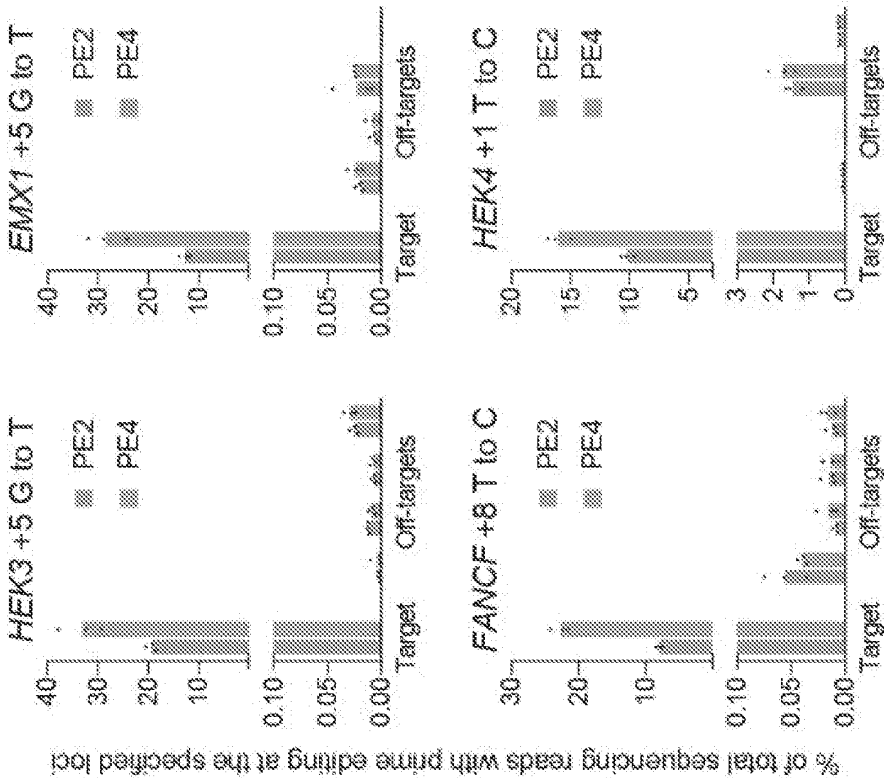


FIG. 53E

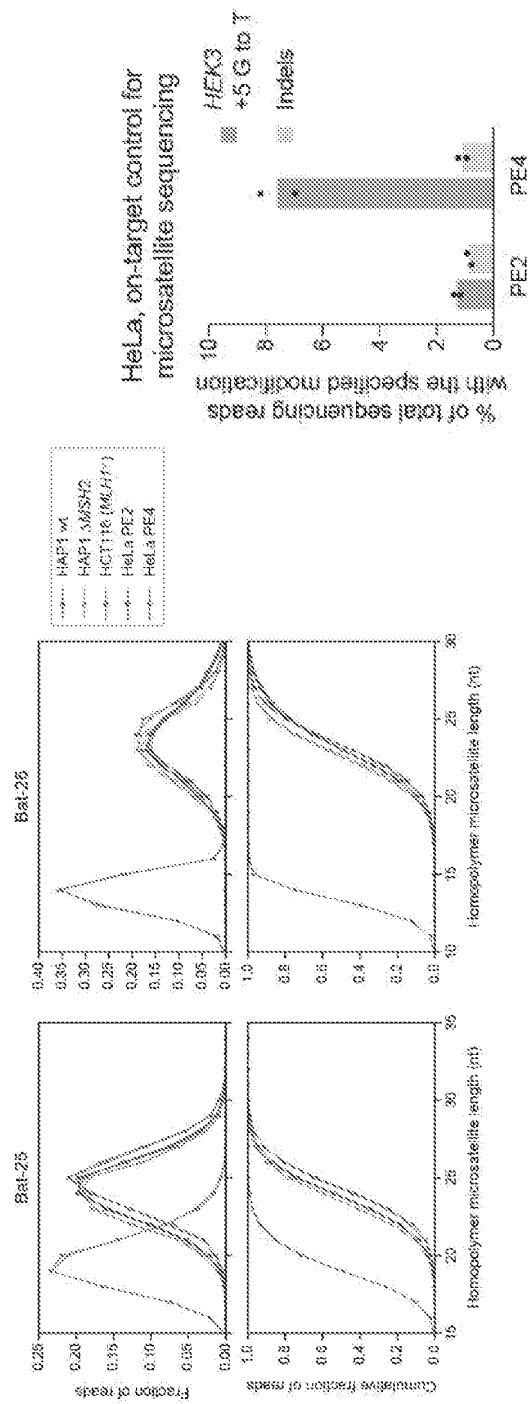


FIG. 53F

FIG. 53G

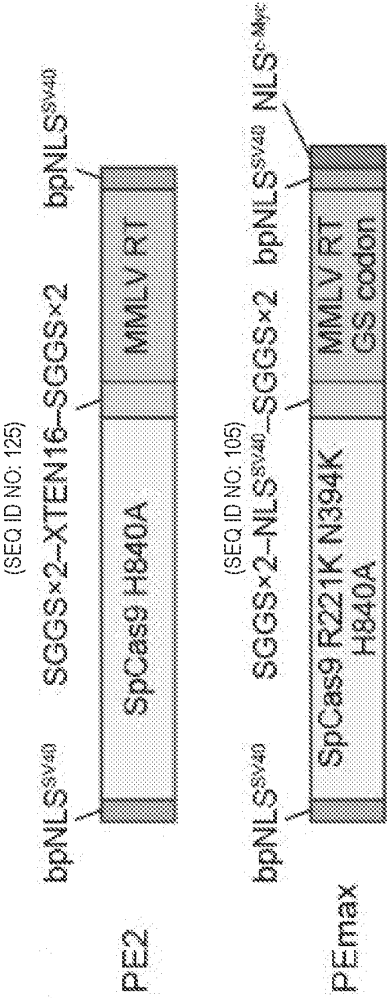


FIG. 54A

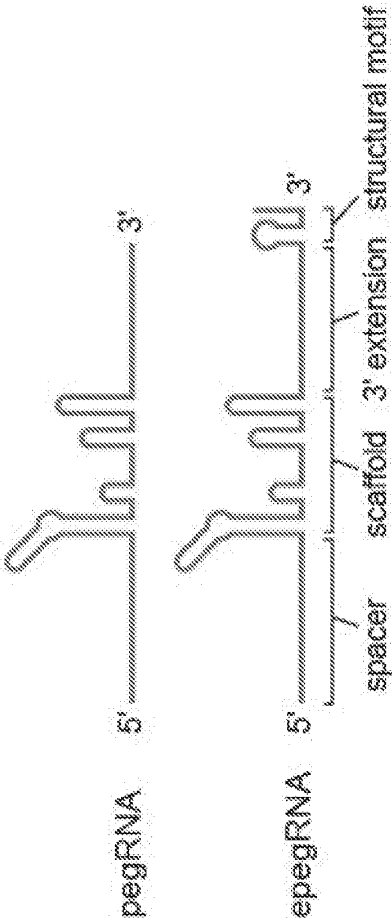


FIG. 54B

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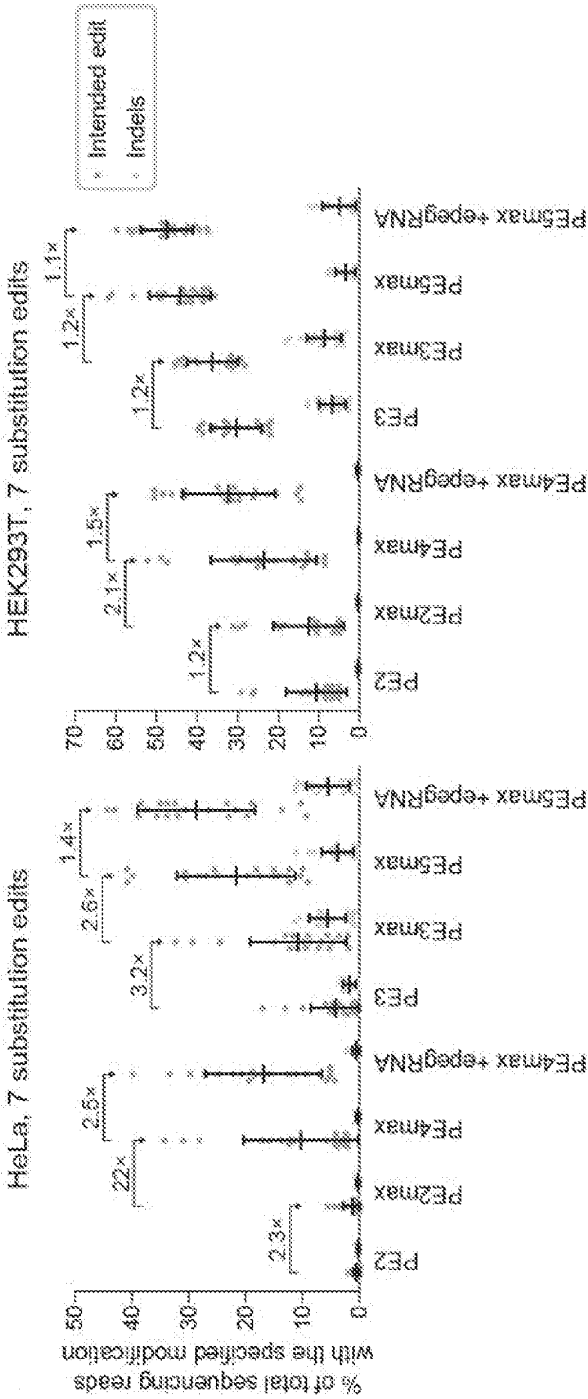


FIG. 54C

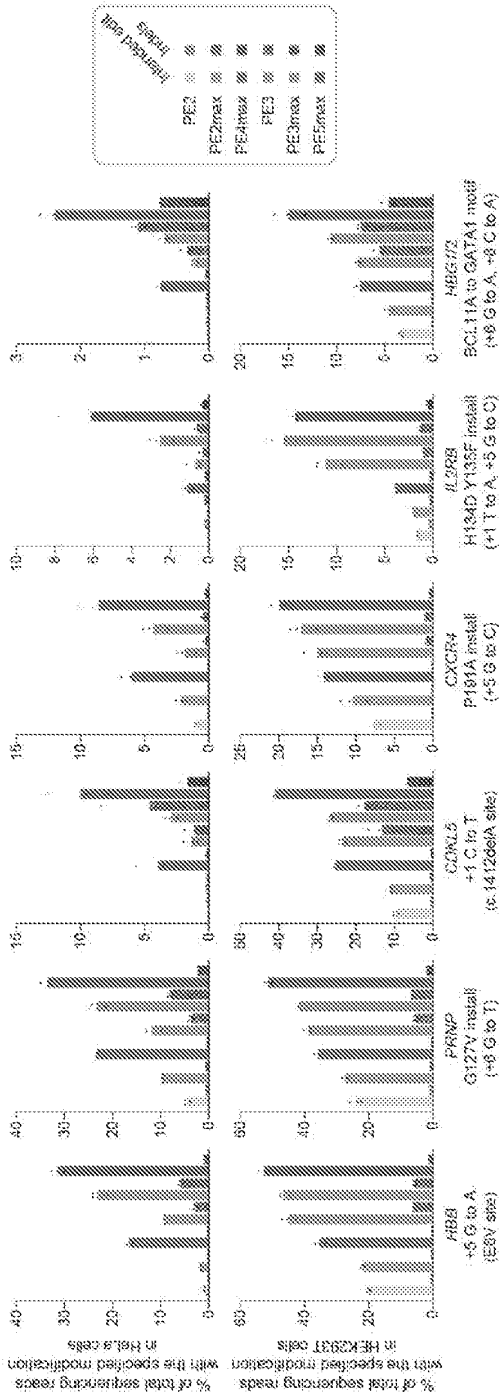


FIG. 54D

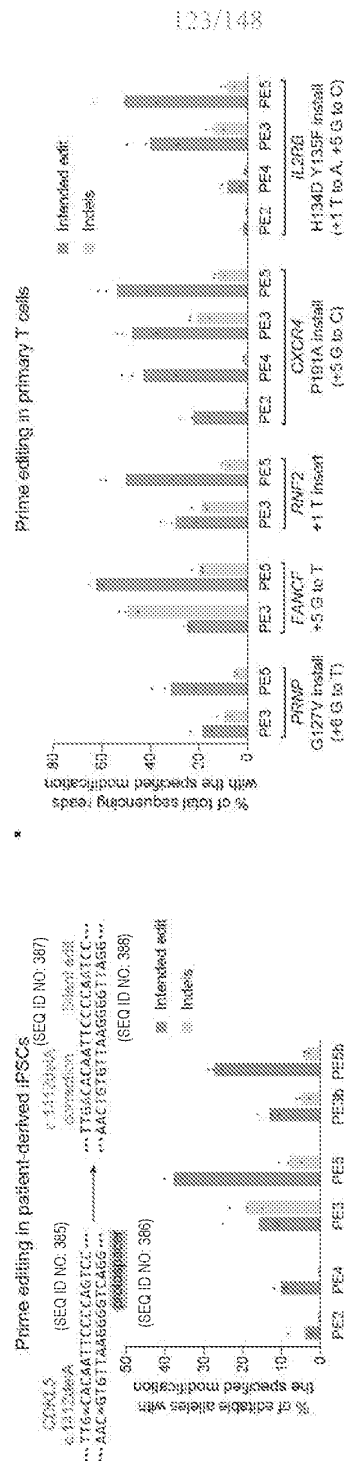


FIG. 54E

FIG. 54F

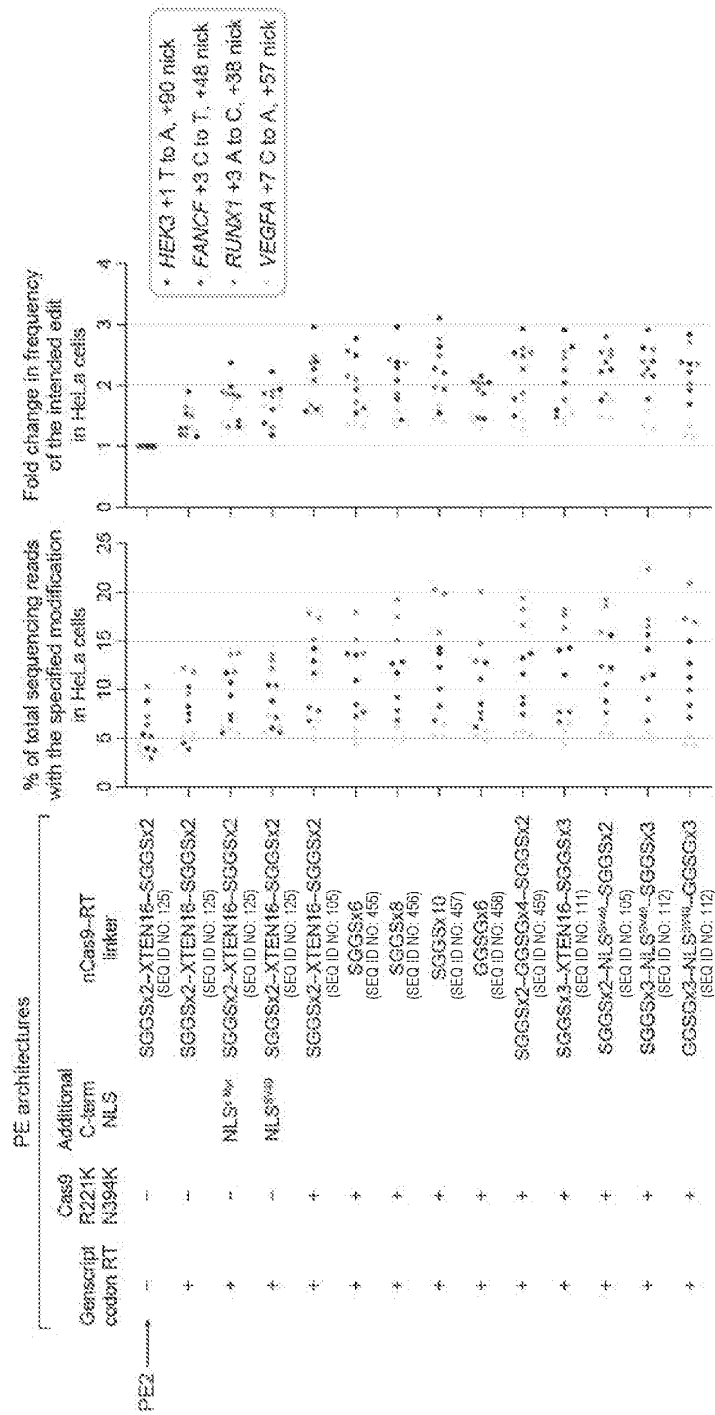


FIG. 55A

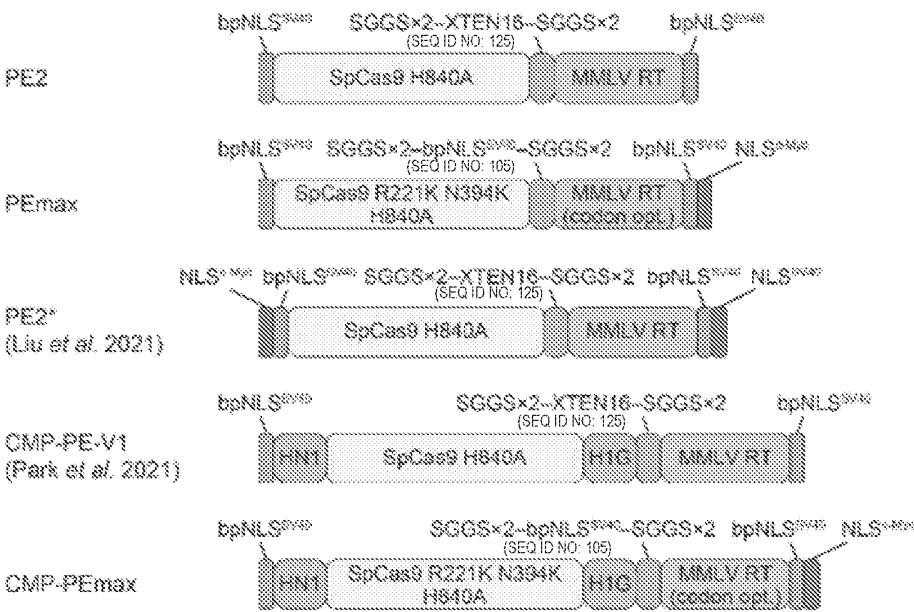


FIG. 56B

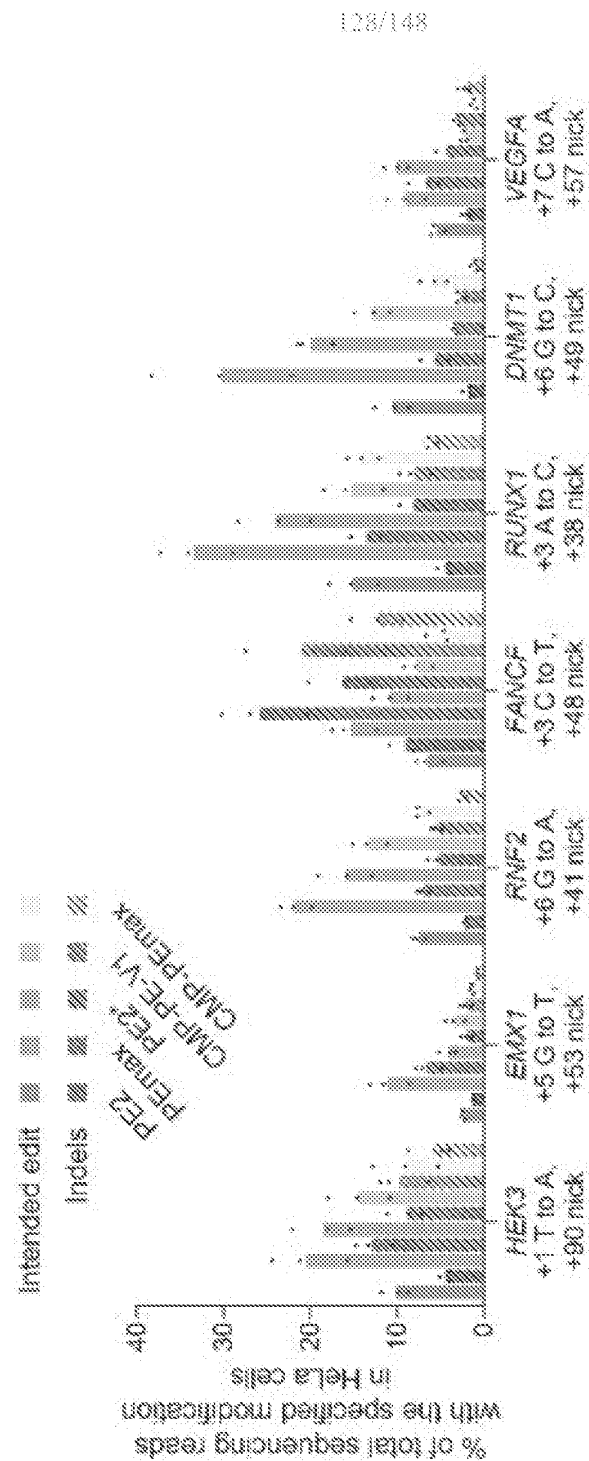


FIG. 56C

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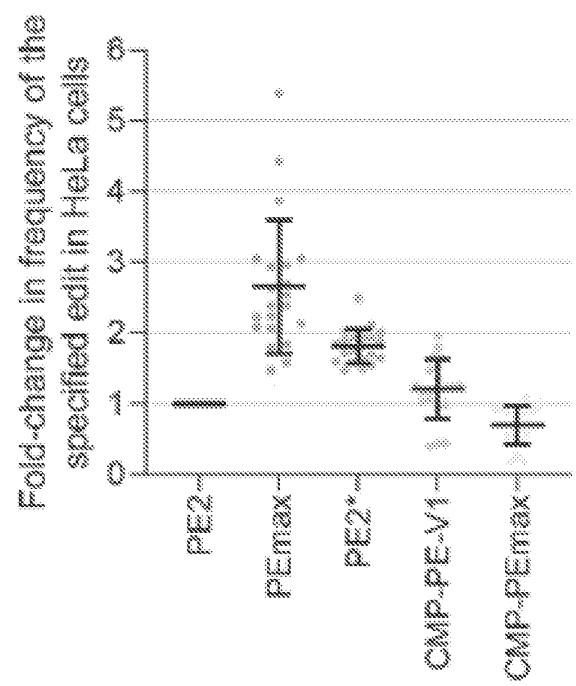


FIG. 56D

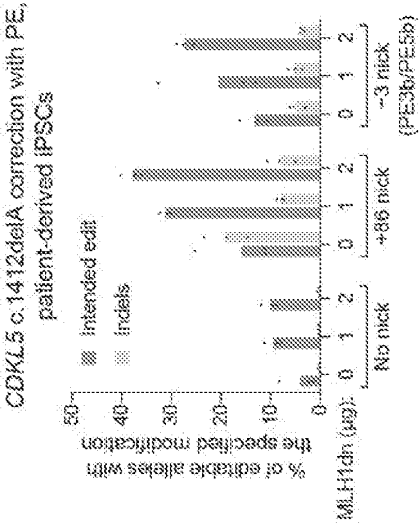


FIG. 56F

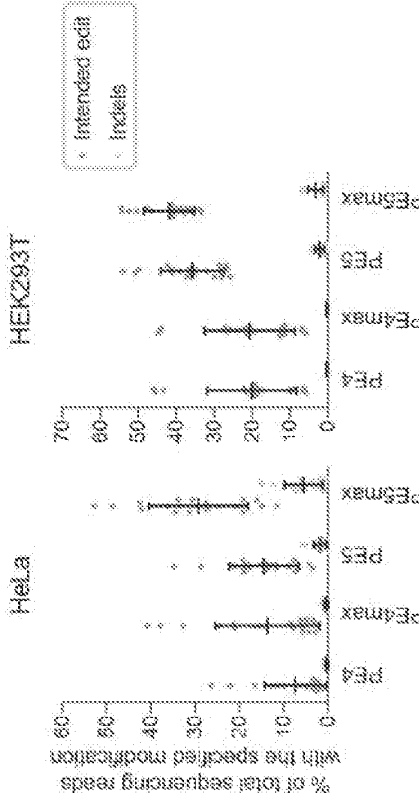
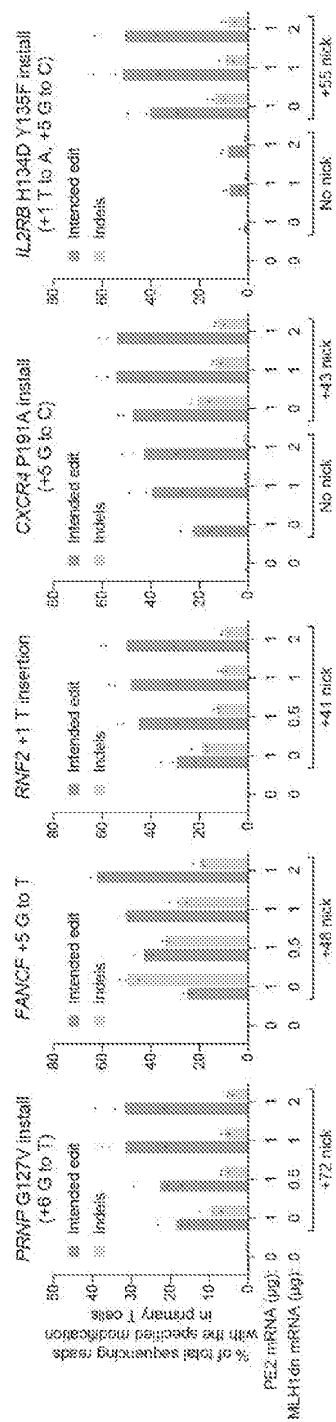


FIG. 56E



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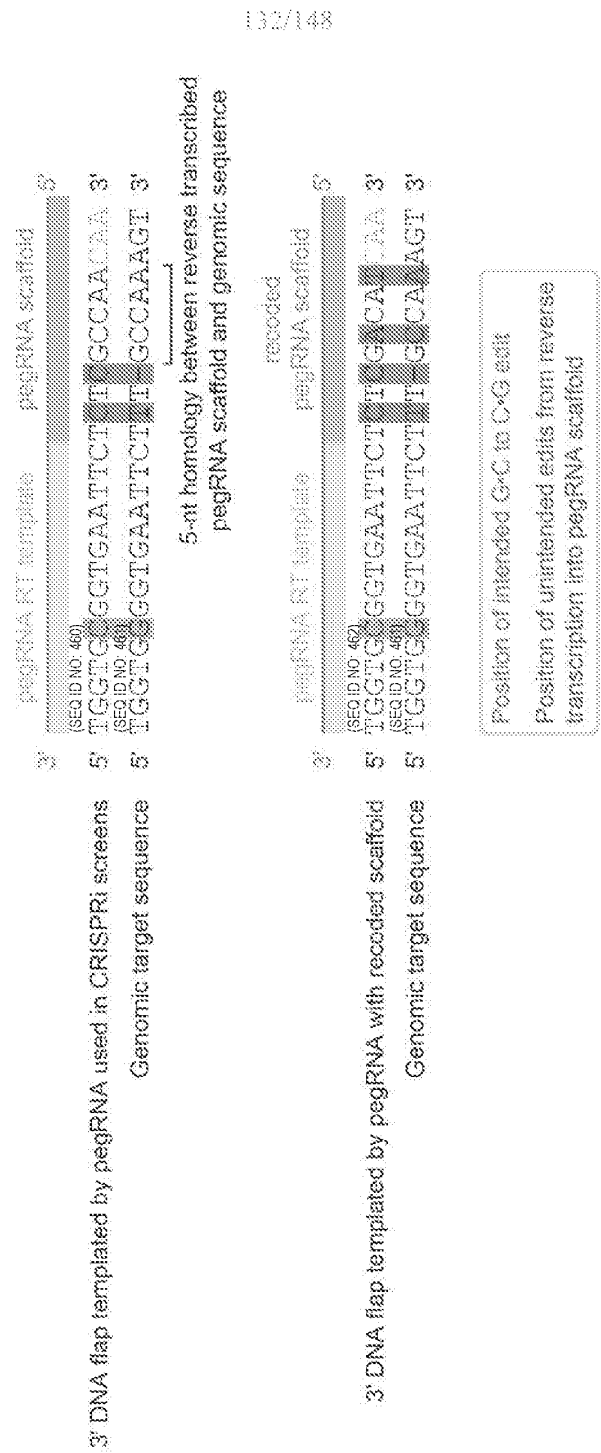


FIG. 57A

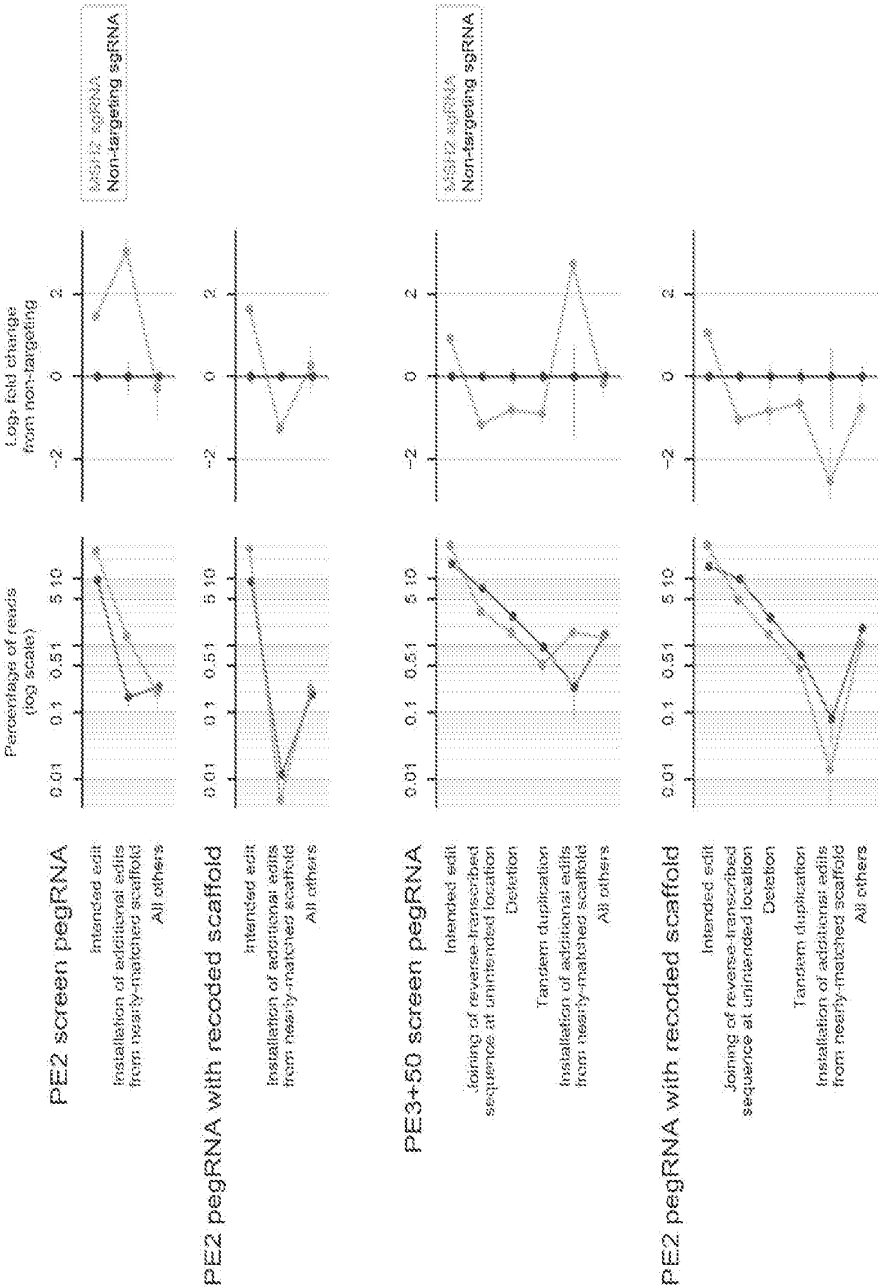


FIG. 57B

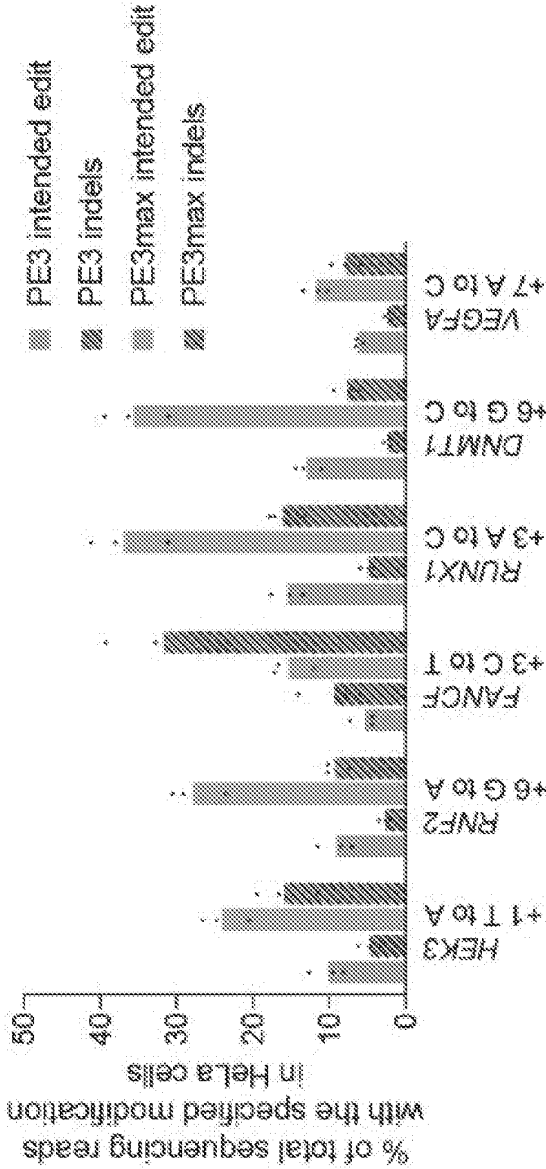


FIG. 58

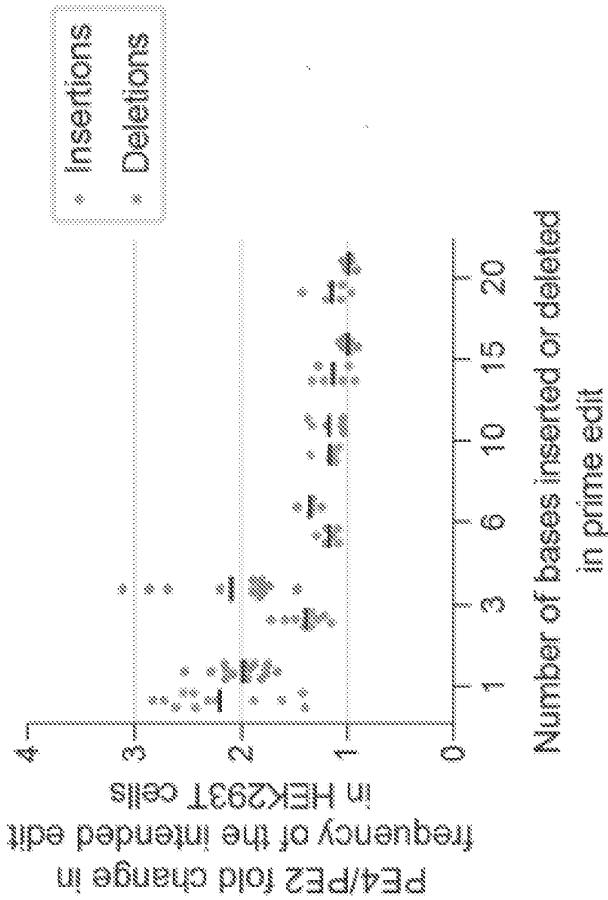


FIG. 59

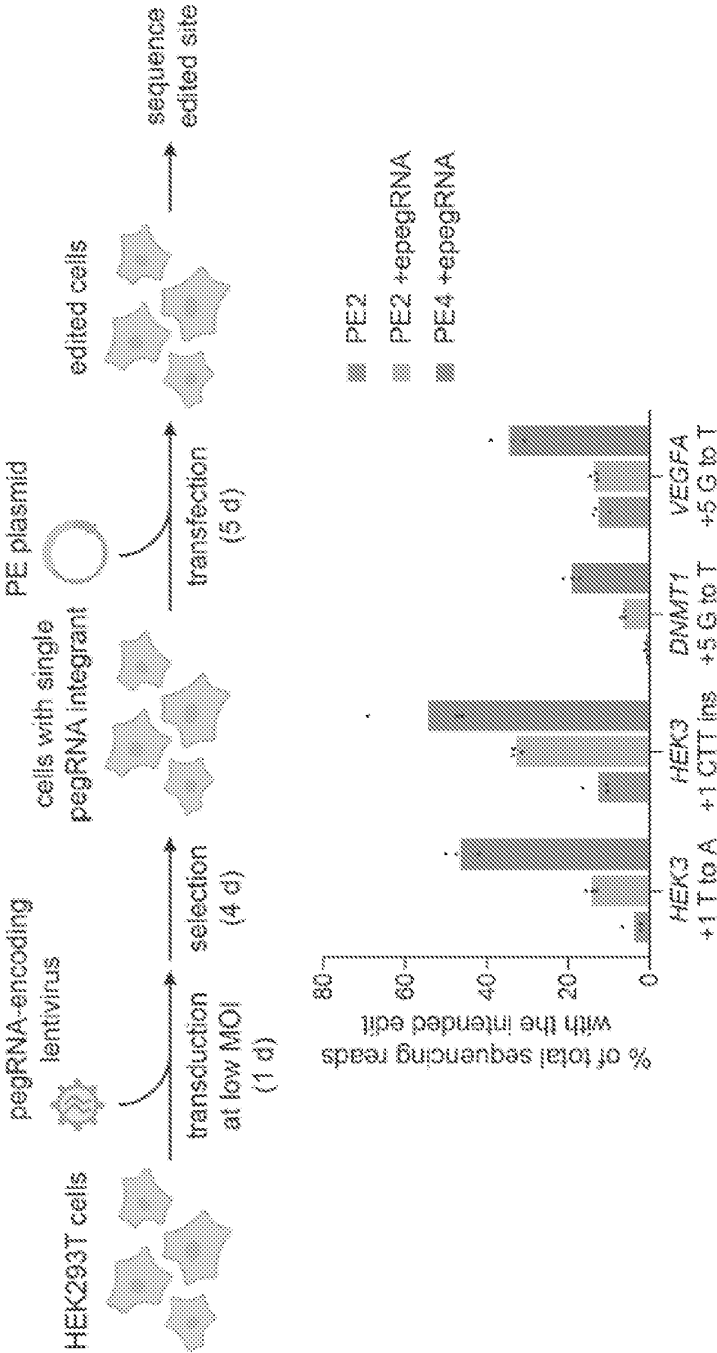


FIG. 60

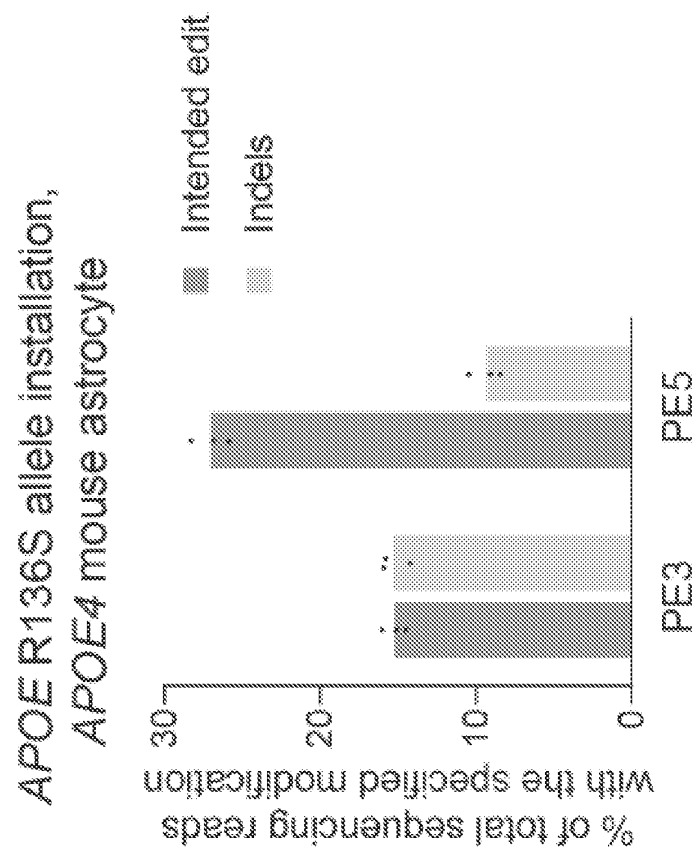


FIG. 61

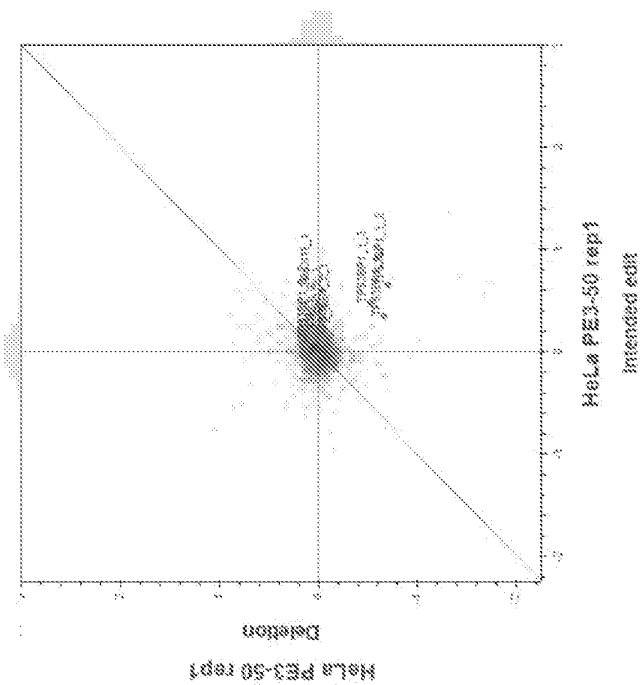


FIG. 62B

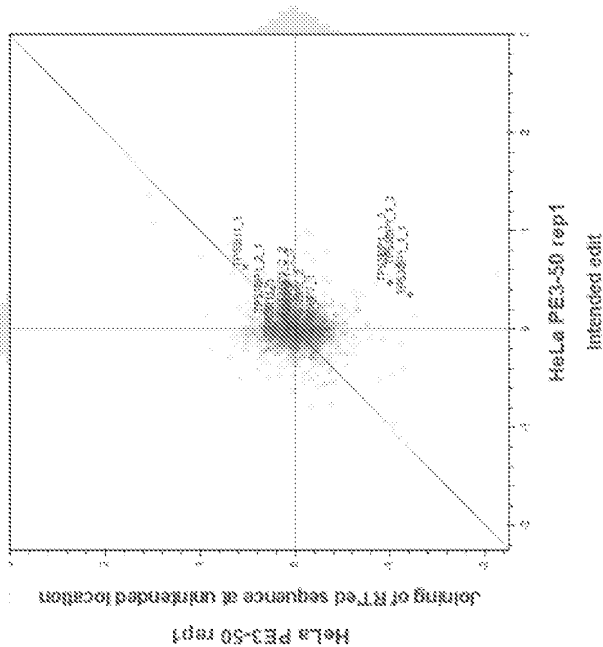


FIG. 62A

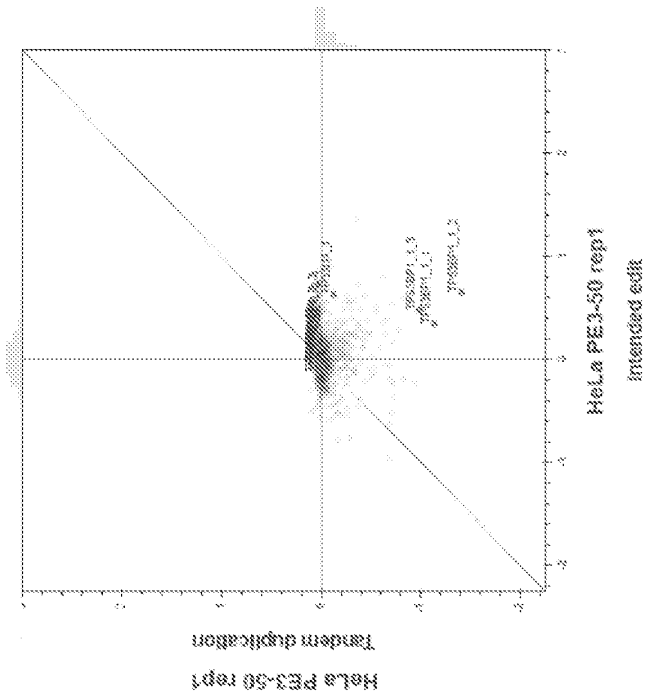


FIG. 62C

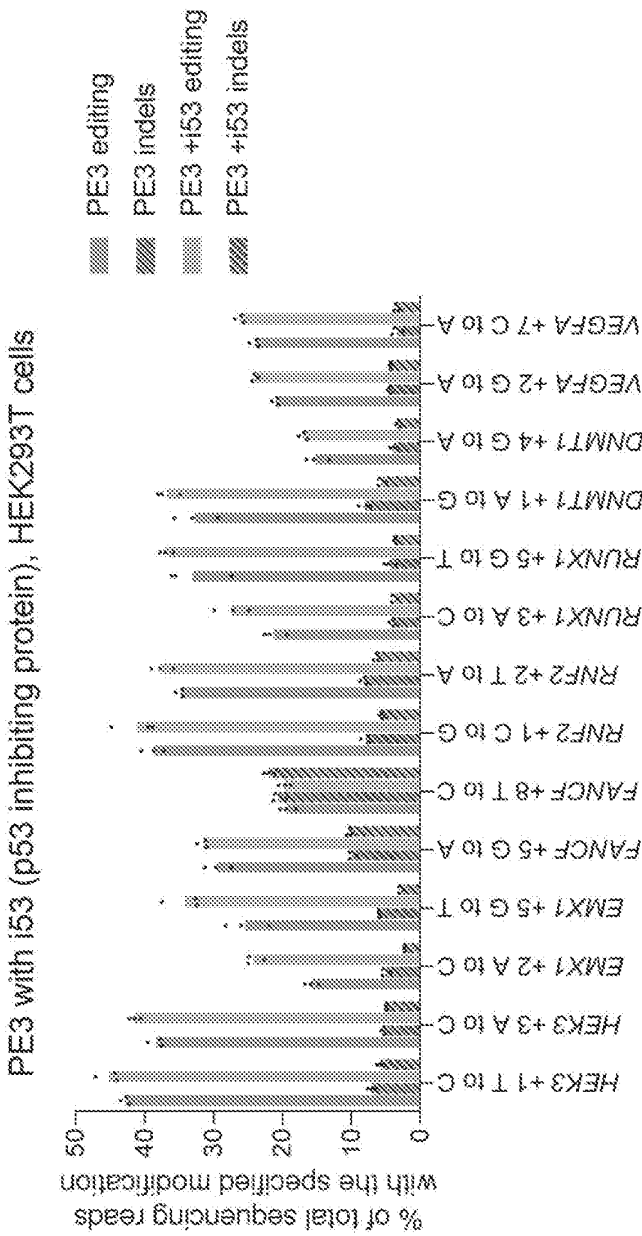


FIG. 63

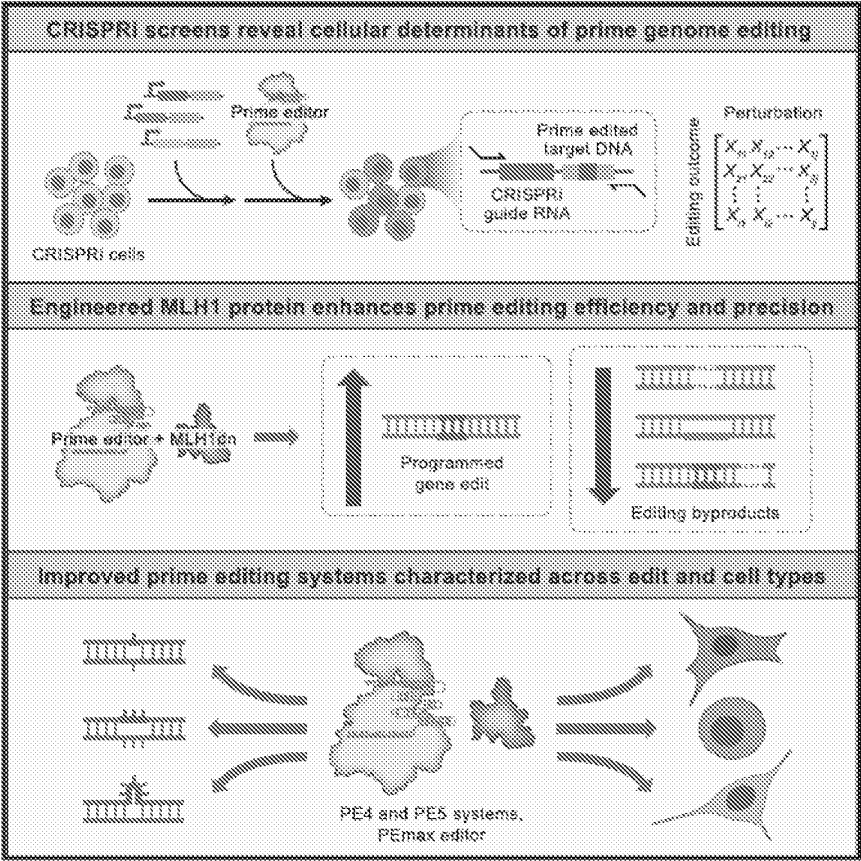
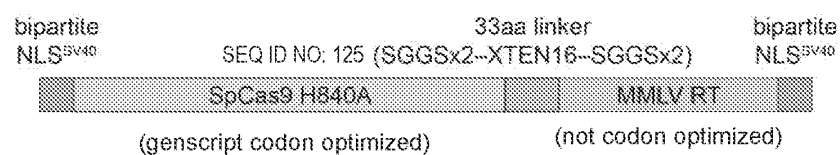


FIG. 64

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Optimization of PE2 protein



1. Codon optimize MMLV RT
2. Mutations to SpCas9 to improve activity
3. Linker optimization
4. Improve nuclear localization

FIG. 65

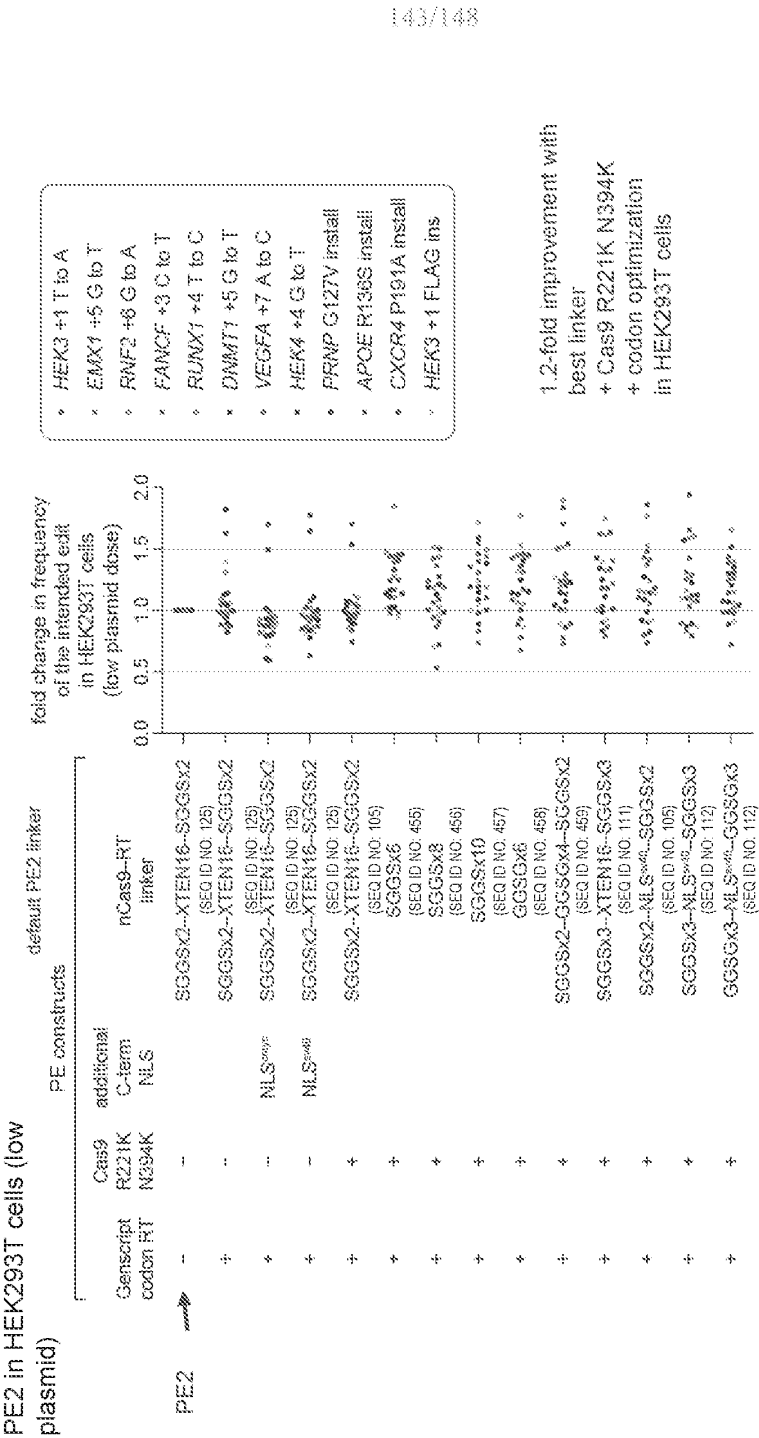


FIG. 66

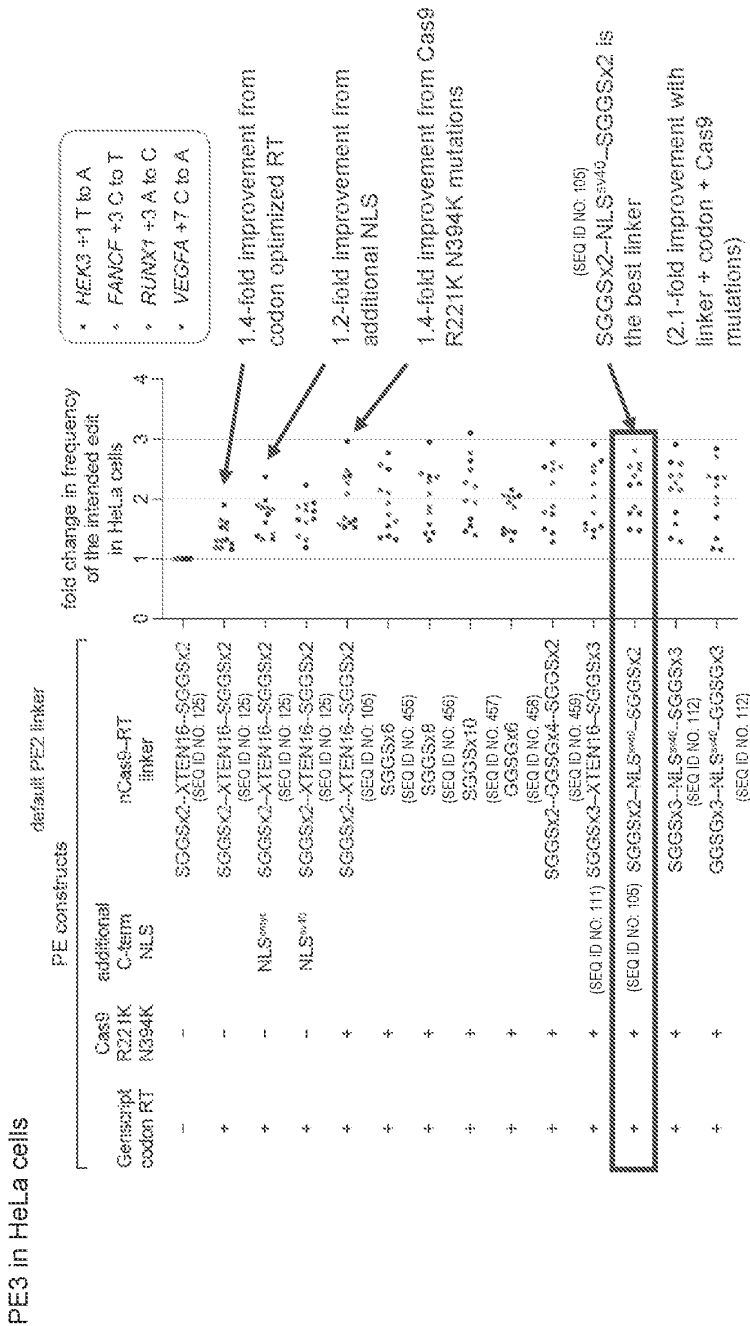
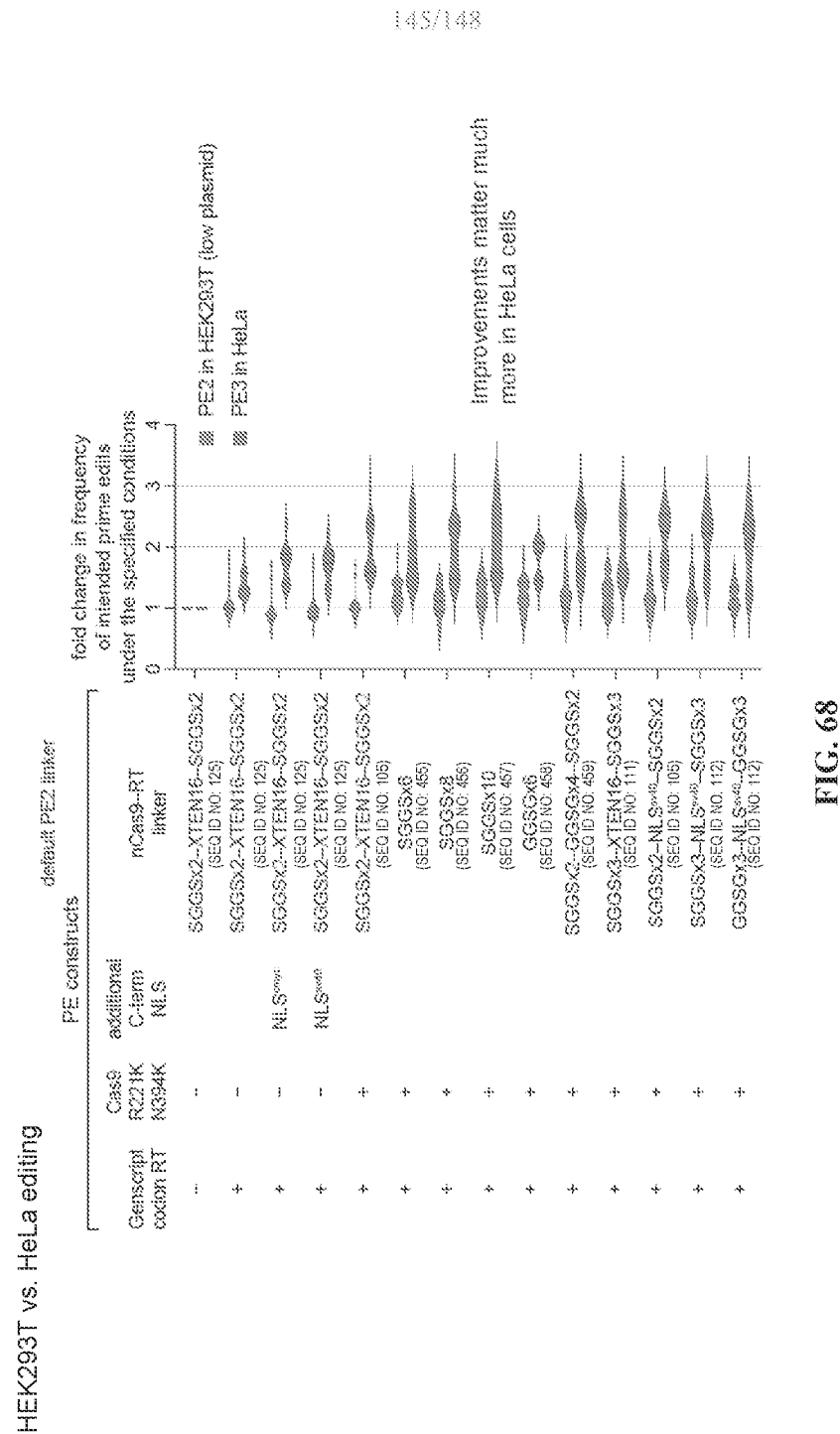
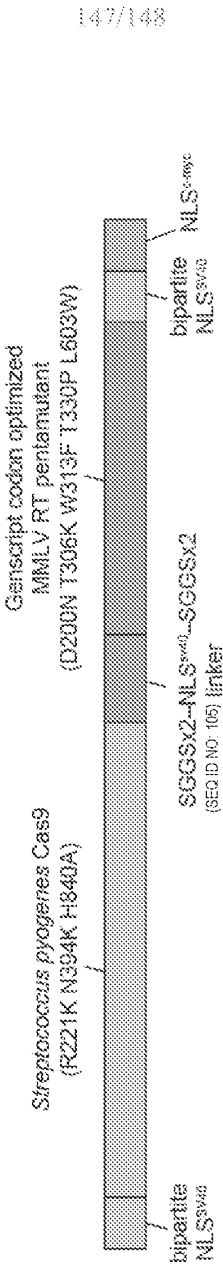


FIG. 67



Final PEmax construct



PEmax improves prime editing efficiency
by 2.59-fold across 6 sites in HeLa cells

FIG. 70

PEmax increases indels in addition to the intended edit

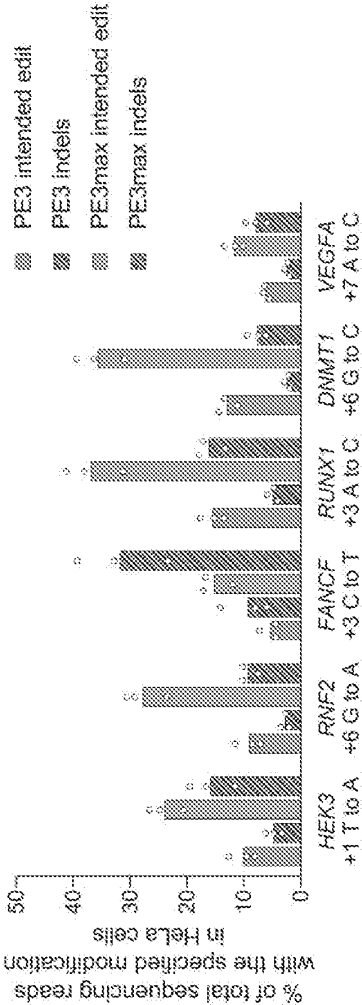


FIG. 71