

CLAIMS

WHAT IS CLAIMED IS:

1. A method of screening a subject for susceptibility to a functional-ATM protein deficiency, wherein the screening comprises determining a presence of a non-thymine variant residue rs609261 located at position -3 relative to a 3' splice site of a NSE (cryptic exon in ATM intron 28) of a human subject's genome, wherein the presence of a non-thymine variant residue rs609261 indicates that the subject has, or is susceptible to, a functional-ATM protein deficiency.
2. A method of selecting a subject for treatment, wherein the subject is susceptible to a functional-ATM protein deficiency, the method comprising determining a presence of a non-thymine variant residue rs609261 located at position -3 relative to a 3' splice site of a NSE (cryptic exon in ATM intron 28) of a human subject's genome, wherein the presence of a non-thymine variant residue rs609261 indicates that the subject has, or is susceptible to, a functional-ATM protein deficiency, and selecting the subject for treatment with an agent thereby increasing a functional-ATM level in the subject.
3. The method according to claim 2, wherein the method further comprises administering the agent to the selected subject, thereby treating the subject.
4. The method according to claim 2 or claim 3, wherein the agent comprises a NSE repressor agent.
5. A method of treatment or prevention of a functional-ATM protein deficiency in a subject, the method comprising identifying a presence of a non-thymine variant residue rs609261 located at position -3 relative to a 3' splice site of NSE (cryptic exon in ATM intron 28) of a human subject's genome, wherein the presence of a non-thymine variant residue rs609261 indicates that the subject has, or is susceptible to, a functional-ATM protein deficiency, and administering an agent to the subject, wherein the agent increases a functional-ATM level.
6. A method of treatment or prevention of a condition associated with a functional-ATM protein deficiency, comprising administering a NSE repressor agent to a subject, thereby increasing a functional ATM protein level, wherein the agent binds to a NSE in ATM intron 28 of a pre-mRNA transcript, thereby decreasing inclusion of the NSE in a mature RNA transcript of the pre-mRNA transcript.
7. The method according to claim 6, wherein the decreasing inclusion of the NSE in the mature RNA transcript increases functional ATM protein expression.

8. The method according to any one of claims 5 to 7, wherein the method is for treatment or prevention of a condition or symptoms associated with a functional-ATM protein deficiency.
9. The method according to claim 8, wherein the condition is ataxia-telangiectasia, cancer, immune deficiency, cellular radiosensitivity or chromosomal instability.
10. The method according to any preceding claim, wherein the NSE comprises a sequence comprising tctacaggttgctgcatagaagaaaag.
11. The method according to any one of claims 4 to 10, wherein the NSE repressor agent binds to the NSE within a sequence comprising
agTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag; or
tcttagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag; or
tctcagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag.
12. The method according to any one of claims 4 to 10, wherein the NSE repressor agent binds to the NSE or s 5' or 3' splice site in ATM intron 28 of the NSE.
13. A method of treatment or prevention of a condition associated with deregulation of ATM expression in a subject comprising administering a NSE-activator agent to the subject, wherein the NSE-activator agent increases inclusion of a NSE in an ATM mature RNA transcript by binding to a regulatory motif in ATM intron 28, or by binding to a U2AF65 binding site upstream of a pseudoexon located 3' of a NSE in ATM intron 28 of an ATM pre-mRNA transcript.
14. A method of treatment or prevention of cancer in a subject comprising administering a NSE-activator agent to the subject, wherein the NSE-activator agent increases a cancer cell's susceptibility to cytotoxic therapy with DNA damaging agents such as radiotherapy, wherein the NSE-activator agent increases inclusion of a NSE in an ATM mature RNA transcript by binding to a regulatory motif in ATM intron 28, or by binding to a U2AF65 binding site upstream of a pseudoexon located 3' of a NSE in ATM intron 28 of an ATM pre-mRNA transcript, and
treating the subject with the cytotoxic therapy, such as radiotherapy or chemotherapy.
15. A method of increasing a cell's susceptibility to cytotoxic therapy with DNA damaging agents such as radiotherapy or chemotherapy comprising reducing ATM protein expression by administering a NSE-activator agent, wherein the NSE-activator agent increases inclusion of a NSE in an ATM mature RNA transcript by binding to motifs in ATM intron 28, or by binding to a U2AF65 binding site upstream of a pseudoexon located 3' of a NSE in ATM intron 28 of an ATM pre-mRNA transcript.

16. The method according to any one of claims 13 to 15, wherein increasing inclusion of the NSE in the mature RNA transcript provides a decrease in functional ATM protein expression.
17. The method according to any one of claims 13 to 16, wherein the pseudoexon comprises the sequence tcatcgaatacttttgaaataag.
18. The method according to any one of claims 13 to 17, wherein the regulatory motif in ATM intron 28 competes with the NSE for spliceosomal components.
19. The method method according to any one of claims 13 to 18, wherein the regulatory motif in ATM intron 28 comprises a 24 nucleotide pseudoexon (PE) located 3' of the NSE in ATM intron 28 of the pre-mRNA transcript.
20. A method of tailoring functional ATM expression in a subject, cell or tissue, comprising administering a NSE-activator agent and/or a NSE-repressor agent described herein.
21. The method according to any preceding claim, wherein the NSE repressor agent and/or NSE activator agent comprises a polynucleic acid polymer.
22. The method according to any preceding claim, wherein the NSE repressor agent and/or NSE activator agent is an SSO (Splice Switching Oligonucleotide).
23. The method according to any preceding claim, wherein the NSE repressor agent and/or NSE activator agent is associated with a delivery vehicle suitable for delivering the NSE repressor agent and/or NSE activator agent to cells.
24. The method according to any one of claims 4 to 12 or 20 to 23, wherein the NSE repressor agent comprises:
 - an SSO of the sequence cuucuaugcagccaaccguagacu (SSO -NSE3), or a nucleic acid analogue thereof; or
 - an SSO of the sequence accuuuuucuucuaugcagccaac (SSO -NSE5), or a nucleic acid analogue thereof; and/or
 - the NSE repressor agent comprises or consists of any one SSO selected from the group comprising: aacauuucuauuuaguuaaaagc (SSO A11); uuaguauuccuugacuuua (SSO A17); gacugguaaaauaaacauauuc (SSO B2); auauauuagagauacauagcc (SSO B4); and uuagagaaucauuuaaaauagac (SSO AN3), or combinations thereof.
25. The method according to any one of claims 13 to 19 wherein the NSE activator agent comprises the SSO PEkr/PEdel; and/or
 - the NSE activator agent comprises or consists of any one SSO selected from the group comprising: aacuuaaagguuauaucuc (SSO A2); uauaaauacgaauaaucga (SSO A4);

caacacgacauaaccaaa (SSO A9); gguaugagaacuauagga (SSO A23); gguaauaagugucacaaa (SSO A25); guaucuacauuagaagg (SSO A26); and uguggggugaccacagcuu (SSO B11), or combinations thereof.

26. Use of rs609261 and/or rs4988000 genotyping for predicting a subject's response to therapy for conditions associated with ATM deregulation.
27. A composition comprising a NSE repressor agent and/or a NSE activator agent described herein.
28. The composition according to claim 27, wherein the composition is a pharmaceutically acceptable formulation.
29. A method of treatment or prevention of a functional-ATM protein deficiency in a subject, the method comprising identifying a presence of a non-thymine variant residue rs609261 located at position -3 relative to a 3' splice site of a NSE (cryptic exon in ATM intron 28) of a human subject's genome,
wherein the presence of the non-thymine variant residue rs609261 indicates that the subject has, or is susceptible to, the functional-ATM protein deficiency, and administering an agent to the subject, wherein the agent replaces the non-thymine variant residue rs609261 with a thymine residue.
30. A method of treatment or prevention of a functional-ATM protein deficiency in a subject, the method comprising replacing a non-thymine variant residue rs609261 located at position -3 relative to the 3' splice site of a NSE (cryptic exon in ATM intron 28) of a human subject's genome with a thymine residue.
31. The method according to claim 29 or claim 30, wherein replacing the non-thymine variant residue rs609261 comprises administration of an agent to the subject, which is arranged to replace the non-thymine variant residue rs609261 with a thymine residue.
32. The method according to any one of claims 29 to 31, wherein the agent for replacement of the non-thymine residue is a genomic editing molecule.
33. The method according to any of claims 29 to 32, wherein the agent for replacement of the non-thymine residue is CRISPR-Cas9, or a functional equivalent thereof, together with an RNA molecule that targets rs609261.
34. A method of treatment or prevention of a functional-ATM protein deficiency in a subject, the method comprising identifying a presence of a guanine variant residue at rs4988000 of a human subject's genome,

wherein the presence of the guanine variant residue at rs4988000 indicates that the subject has, or is susceptible to, the functional-ATM protein deficiency, and administering an agent to the subject, wherein the agent replaces the guanine variant residue at rs4988000 with an adenine.

35. A method of treatment or prevention of a functional-ATM protein deficiency in a subject, the method comprising replacing a guanine variant residue at rs4988000 of a human subject's genome with an adenine residue, or blocking the guanine variant residue at rs4988000 by the binding an SSO to the guanine variant residue at rs4988000.
36. The method according to claim 34 or claim 35, wherein replacing the guanine variant residue at rs4988000 comprises administration of an agent to the subject, which is arranged to replace the guanine variant residue at rs4988000 with an adenine residue.
37. The method according to any one of claims 34 to 36, wherein the agent for replacement of the guanine residue is a genomic editing molecule.
38. The method according to any one of claims 31 to 34, wherein the agent for replacement of the guanine residue is CRISPR-Cas9, or a functional equivalent thereof, together with an RNA molecule that targets rs4988000.
39. A method of screening a subject or a population of subjects for susceptibility to a functional-ATM protein deficiency, wherein the screening comprises determining a presence of a guanine variant residue at rs4988000 of a human subject's genome, wherein the presence of a guanine variant residue at rs4988000 indicates that the subject (or group of subjects) has, or is susceptible to, functional-ATM protein deficiency.
40. A method of selecting a subject or a population of subjects for treatment or prophylaxis, wherein the subject is susceptible to a functional-ATM protein deficiency, the method comprising determining a presence of a guanine variant residue at rs4988000 of a human subject's genome, wherein the presence of a guanine variant residue at rs4988000 indicates that the subject has, or is susceptible to, the functional-ATM protein deficiency, and selecting the subject for treatment with an agent that increases functional-ATM levels in the subject.
41. A method of treatment or prevention of functional-ATM protein deficiency in a subject, the method comprising identifying a presence of a guanine variant residue at rs4988000 of a human subject's genome,

wherein the presence of a guanine variant residue at rs4988000 indicates that the subject has, or is susceptible to, the functional-ATM protein deficiency, and administering an agent to the subject, wherein the agent increases functional-ATM levels.

42. The method of any one of claims 29-33 and any one of claims 34-38 in combination to modify a CG haplotype to TA.
43. The method of claim 1 and claim 36 in combination to identify a CG haplotype in a subject, and optionally to treat or to select a subject for treatment according to any preceding claim.
44. A method of modifying regulation of inclusion of a NSE in a mature RNA transcript, the method comprising inserting or deleting one or more splicing regulatory motifs upstream or downstream of the NSE that compete with the NSE for spliceosomal components, said one or more splicing regulatory motifs comprising a cryptic splice site or a pseudo-exon.
45. A method of modifying regulation of expression of a functional protein, wherein the expression of a functional protein is regulated by inclusion of a NSE in a mature RNA transcript of a gene encoding the functional protein, the method comprising inserting or deleting one or more splicing regulatory motifs upstream or downstream of the NSE that compete with the NSE for spliceosomal components, said one or more splicing regulatory motifs comprising cryptic splice sites or pseudo-exons.
46. The method according to claim 44 or 45, wherein the insertion or the deletion of the one or more splicing regulatory motifs is in genomic DNA of ATM intron 28.
47. The method according to any of claims 44 to 46, wherein insertion of the one or more splicing regulatory motifs causes a reduction in the inclusion of the NSE in the mature RNA transcript.
48. The method according to any of claims 44 to 46, wherein the deletion of the one or more splicing regulatory motifs causes an increase in the inclusion of the NSE in the mature RNA transcript.
49. The method according to any one of claims 44 to 48, wherein the insertion or the deletion of the one or more splicing regulatory motifs comprises the use of genome editing technology, such as CRISPR-Cas9.
50. A kit comprising one or more oligonucleotide probes for identifying rs609261 and/or rs4988000 variants.
51. The kit according to claim 50, wherein the one or more oligonucleotide probes are primers for use in PCR amplifying a region of nucleic acid comprising the rs609261 and/or the rs4988000 variants.

52. A vector comprising a nucleic acid encoding a NSE activating agent and/or a NSE repressor agent.
53. A method of screening for an agent capable of modifying regulation of expression of a gene comprising:
- identifying a nonsense-mediated RNA decay switch exon (NSE) that limits functional gene expression;
 - identifying one or more splicing regulatory motifs upstream or downstream of the NSE that compete with the NSE for spliceosomal components, said one or more splicing regulatory motifs comprising cryptic splice sites or pseudoexons;
 - targeting the one or more splicing regulatory motifs with an antisense polynucleic acid comprising a sequence that hybridizes to a splicing regulatory motif of the one or more splicing regulatory motifs through Watson-Crick base pairing; and
 - determining if there is an increased or decreased inclusion of the NSE in a mature RNA transcript of the gene.
54. A method of modulating expression of a gene comprising providing an agent that binds to a splicing regulatory motif, such as a cryptic splice site or a pseudoexon, that competes with a nonsense-mediated RNA decay switch exon (NSE) for spliceosomal components.
55. An agent that binds to a gene splicing regulatory motif, such as a cryptic splice site or a pseudoexon, that competes with a nonsense-mediated RNA decay switch exon (NSE) for spliceosomal components, wherein the gene splicing regulatory motif controls inclusion of the NSE into a mature RNA transcript of the gene.
56. A method, use, composition, vector, or agent substantially described herein, optionally with reference to the accompanying figures.
57. A method of modulating protein expression comprising:
- a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif on a pre-processed mRNA transcript, wherein a hybridization of the contacted polynucleic acid polymer to the target motif either promotes or represses activation of a non-sense mediated RNA decay switch exon (NSE);
 - c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the NSE is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the NSE modulates protein expression.

58. The method of claim 57, wherein the protein is expressed from the processed mRNA transcript.
59. The method of claim 57, wherein the presence of the NSE downregulates protein expression.
60. The method of claim 57, wherein the absence of the NSE upregulates protein expression.
61. The method of claim 57, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
62. The method of claim 61, wherein the motif is a splicing regulatory motif that competes with the NSE for a spliceosomal component.
63. The method of claim 62, wherein the splicing regulatory motif comprises a cryptic splice site or a pseudoexon.
64. The method of claim 63, wherein the pseudoexon is a 24 nucleotide pseudoexon located at 3' of a NSE in ATM intron 28 of the pre-mRNA transcript.
65. The method of claim 62, wherein the motif is a U2AF65 binding site.
66. The method of claim 62, wherein the motif is a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
67. The method of claim 66, wherein the transposed element is Alu or MER51.
68. The method of claim 67, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
69. The method of claim 67, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
70. The method of claim 67, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
71. The method of any one of claims 57-70, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
72. The method of any one of claims 57-71, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
73. A method of modulating protein expression comprising:
 - a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif within a transposed element, wherein a hybridization of the contacted polynucleic acid polymer to the target motif either promotes or represses activation of a non-sense mediated RNA decay switch exon (NSE);

- c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the NSE is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the NSE modulates protein expression.
74. A method of modulating protein expression comprising:
- a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif either upstream or downstream of a transposed element, wherein a hybridization of the contacted polynucleic acid polymer to the target motif promotes or represses activation of a non-sense mediated RNA decay switch exon (NSE);
 - c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the NSE is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the NSE modulates protein expression.
75. The method of claim 73 or 74, wherein the protein is expressed from the processed mRNA transcript.
76. The method of claim 73 or 74, wherein the presence of the NSE downregulates protein expression.
77. The method of claim 73 or 74, wherein the absence of the NSE upregulates protein expression.
78. The method of claim 73 or 74, wherein the transposed element is Alu or MER51.
79. The method of claim 73 or 74, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
80. The method of any one of the claims 73, 74 or 79, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
81. The method of claim 73, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
82. The method of claim 74, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
83. The method of claim 74, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
84. The method of claim 73 or 74, wherein activation of the NSE further induces exon skipping.

85. The method of any one of the claims 73, 74 or 84, wherein the NSE is located in intron 28.
86. The method of any one of the claims 73, 74, 84 or 85, wherein the NSE modulates ATM protein expression.
87. A method of treating or preventing a disease or condition associated with deregulation of ATM expression in a subject in need thereof, the method comprising:
administering to the subject a pharmaceutical composition comprising:
(i) a non-sense mediated RNA decay switch exon (NSE)-activator agent that interacts with a pre-processed mRNA transcript to promote inclusion of a NSE into a processed mRNA transcript; and
(ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;
wherein the disease or condition associated with deregulation of ATM expression is treated or prevented in the subject by the administration of the NSE-activator agent.
88. A method of treating or preventing a disease or condition associated with a functional-ATM protein deficiency in a subject in need thereof, the method comprising:
administering to the subject a pharmaceutical composition comprising:
(i) a non-sense mediated RNA decay switch exon (NSE)-repressor agent that interacts with a pre-processed mRNA transcript to promote exclusion of a NSE into a processed mRNA transcript; and
(ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;
wherein the disease or condition associated with a functional-ATM protein deficiency is treated or prevented in the subject by the administration of the NSE-repressor agent.
89. The method of claim 87, wherein the NSE-activator agent is an isolated polynucleic acid polymer.
90. The method of claim 88, wherein the NSE-repressor agent is an isolated polynucleic acid polymer.
91. The method of claim 89 or 90, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
92. The method of claim 89, wherein the polynucleic acid polymer hybridizes to a splicing regulatory motif that competes with the NSE for spliceosomal components.
93. The method of claim 92, wherein the splicing regulatory motif comprises a cryptic splice site or a pseudoexon.
94. The method of claim 93, wherein the pseudoexon is a 24 nucleotide pseudoexon located at 3' of a NSE in ATM intron 28 of the pre-mRNA transcript.

95. The method of claim 89, wherein the polynucleic acid polymer hybridizes to a U2AF65 binding site.
96. The method of claim 89 or 90, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
97. The method of claim 96, wherein the transposed element is Alu or MER51.
98. The method of claim 97, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
99. The method of claim 97, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
100. The method of claim 97, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
101. The method of any one of the claims 89-100, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
102. The method of any one of the claims 89-101, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
103. The method of claim 87, wherein the disease or condition is cancer.
104. A method of treating or preventing a disease or condition in a subject in need thereof, the method comprising:
 - administering to the subject a pharmaceutical composition comprising:
 - (i) a non-sense mediated RNA decay switch exon (NSE)-activator agent that interacts with a pre-processed mRNA transcript to promote inclusion of NSE into a processed mRNA transcript; and
 - (ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;wherein the disease or condition is treated or prevented in the subject by the administration of the NSE-activator agent.
105. A method of treating or preventing a disease or condition in a subject in need thereof, the method comprising:
 - administering to the subject a pharmaceutical composition comprising:
 - (i) a non-sense mediated RNA decay switch exon (NSE)-repressor agent that interacts with a pre-processed mRNA transcript to promote exclusion of an NSE into a processed mRNA transcript; and

- (ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;
wherein the disease or condition is treated or prevented in the subject by the administration of the NSE-repressor agent.
106. The method of claim 104, wherein the NSE-activator agent is an isolated polynucleic acid polymer.
107. The method of claim 105, wherein the NSE-repressor agent is an isolated polynucleic acid polymer.
108. The method of claim 106 or 107, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
109. The method of claim 106, wherein the polynucleic acid polymer hybridizes to a splicing regulatory motif that competes with the NSE for spliceosomal components.
110. The method of claim 109, wherein the splicing regulatory motif comprises a cryptic splice site or a pseudoexon.
111. The method of claim 110, wherein the pseudoexon is a 24 nucleotide pseudoexon located at 3' of a NSE in ATM intron 28 of the pre-mRNA transcript.
112. The method of claim 108, wherein the polynucleic acid polymer hybridizes to a U2AF65 binding site.
113. The method of claim 106 or 107, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
114. The method of claim 113, wherein the transposed element is Alu or MER51.
115. The method of claim 114, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
116. The method of claim 114, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
117. The method of claim 114, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
118. The method of any one of the claims 104-117, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
119. The method of any one of the claims 104-118, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
120. The method of claim 104, wherein the disease or condition is cancer.

121. The method of claim 104, wherein the disease or condition is a disease or condition associated with deregulation of ATM expression.
122. The method of claim 105, wherein the disease or condition is a disease or condition associated with a functional-ATM protein deficiency.
123. The method of any one of the claims 57-122, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.
124. The method of any one of the claims 57-123, wherein the polynucleic acid polymer comprises an artificial nucleotide.
125. The method of claim 124, wherein the artificial nucleotide is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), a 1',5' - anhydrohexitol nucleic acid (HNA), a morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.
126. The method of claim 87, 88, 104 or 105, wherein the delivery vehicle comprises a nanoparticle-based delivery vehicle.
127. A method of modulating protein expression comprising:
 - a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif within a transposed element, wherein a hybridization of the contacted polynucleic acid polymer to the target motif either promotes or represses activation of an alternative splice site;
 - c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the alternative splice site is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the alternative splice site modulates protein expression.
128. A method of modulating protein expression comprising:
 - a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif either upstream or downstream of a transposed element, wherein a hybridization of the contacted

- polynucleic acid polymer to the target motif promotes or represses activation of an alternative splice site;
- c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the alternative splice site is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the alternative splice site modulates protein expression.
129. The method of claim 127 or 128, wherein the transposon element is on the pre-processed mRNA transcript.
130. A method of modulating protein expression comprising:
- a) contacting an isolated polynucleic acid polymer to a target cell of a subject;
 - b) hybridizing the contacted polynucleic acid polymer to a target motif on a pre-processed mRNA transcript, wherein hybridization of the contacted polynucleic acid polymer to the target motif either promotes or represses activation of an alternative splice site;
 - c) processing a mRNA transcript of the pre-processed mRNA transcript, wherein the alternative splice site is either present or absent in the mRNA transcript; and
 - d) translating the processed mRNA transcript of step c), wherein the presence or absence of the alternative splice site modulates protein expression.
131. The method of claim 130, wherein the protein is expressed from the processed mRNA transcript.
132. The method of claim 130, wherein the presence of NSE downregulates protein expression.
133. The method of claim 130, wherein the absence of NSE upregulates protein expression.
134. The method of claim 130, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
135. The method of claim 134, wherein the motif is a splicing regulatory motif that competes with NSE for a spliceosomal component.
136. The method of claim 135, wherein the splicing regulatory motif comprises a cryptic splice site or a pseudoexon.
137. The method of claim 136, wherein the pseudoexon is a 24 nucleotide pseudoexon located at 3' of a NSE in ATM intron 28 of the pre-mRNA transcript.
138. The method of claim 134, wherein the motif is a U2AF65 binding site.
139. The method of claim 134, wherein the motif is a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.

140. The method of claim 139, wherein the transposed element is Alu or MER51.
141. The method of claim 140, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
142. The method of claim 140, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
143. The method of claim 140, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
144. The method of any one of the claims 130-143, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
145. The method of any one of the claims 130-144, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
146. A pharmaceutical composition comprising:
 - a) a non-sense mediated RNA decay switch exon (NSE)-activator agent that interacts with a pre-processed mRNA transcript to promote inclusion of NSE into a processed mRNA transcript, or a non-sense mediated RNA decay switch exon (NSE)-repressor agent that interacts with a pre-processed mRNA transcript to promote exclusion of an NSE into a processed mRNA transcript; and
 - b) a pharmaceutically acceptable excipient and/or a delivery vehicle.
147. The pharmaceutical composition of claim 146, wherein the NSE-activator agent is an isolated polynucleic acid polymer.
148. The pharmaceutical composition of claim 147, wherein the NSE-repressor agent is an isolated polynucleic acid polymer.
149. The pharmaceutical composition of claim 147 or 148, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
150. The pharmaceutical composition of claim 147, wherein the polynucleic acid polymer hybridizes to a splicing regulatory motif that competes with the NSE for a spliceosomal component.
151. The pharmaceutical composition of claim 150, wherein the splicing regulatory motif comprises a cryptic splice site or a pseudoexon.
152. The pharmaceutical composition of claim 151, wherein the pseudoexon is a 24 nucleotide pseudoexon located at 3' of NSE in ATM intron 28 of the pre-mRNA transcript.

153. The pharmaceutical composition of claim 150, wherein the polynucleic acid polymer hybridizes to a U2AF65 binding site.
154. The pharmaceutical composition of claim 147 or 148, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
155. The pharmaceutical composition of claim 154, wherein the transposed element is Alu or MER51.
156. The pharmaceutical composition of claim 154, wherein the isolated polynucleic acid polymer hybridizes to a target motif within Alu.
157. The pharmaceutical composition of claim 154, wherein the isolated polynucleic acid polymer hybridizes to a target motif that is either upstream or downstream of Alu.
158. The pharmaceutical composition of claim 154, wherein the isolated polynucleic acid polymer hybridizes to a target motif downstream of MER51.
159. The pharmaceutical composition of any one of the claims 146-158, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.
160. The pharmaceutical composition of any one of the claims 146-159, wherein the isolated polynucleic acid polymer comprises a sequence with at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 18-52.
161. A cell comprising the pharmaceutical composition of any one of claims 146-160.