

CLAIMS

What is claimed is:

1. ~~A~~An in-vitro method of modulating expression of ~~a target protein~~polycystin in a cell ~~having a pre-mRNA that is transcribed from a target gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD-exon);~~the method comprising contacting the cell a composition that comprises an agent or a vector encoding the agent~~to the cell, wherein the agent comprises a sequence that is the reverse complement sequence of a target sequence of a pre-mRNA,~~ whereby binding of the agent to the target sequence modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating the expression of ~~the target protein~~polycystin in the cell, wherein the ~~target protein~~polycystin is encoded by a *PKD2* gene.
2. ~~A method of treating or reducing the likelihood of developing a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject,~~comprising~~contacting an agent or a vector encoding the agent~~to the cell of the subject, whereby, wherein the agent ~~modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD-exon) from~~comprises a sequence that is the reverse complement sequence of a target sequence of a pre-mRNA, wherein the agent (a) binds to a target sequence of the pre-mRNA that is transcribed from a target gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD exon), and (b) modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating ~~the~~ expression of ~~the~~ target protein in ~~the~~ cell ~~of~~having the subject~~pre-mRNA,~~ wherein the ~~target protein~~pre-mRNA is encoded by a *PKD2* gene.
3. ~~The method of claim 1 or 2, wherein the target protein is polycystin 2.~~
4. ~~The method of claim 2, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin 2.~~
5. ~~The method of claim 2, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin 1.~~
6. ~~The method of claim 3, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of a protein that polycystin 2 functionally augments, compensates for, replaces, or functionally interacts with.~~
7. ~~The method of any one of claims 1-6, wherein the agent:~~
 - ~~(a) binds to a targeted portion of the pre-mRNA;~~
 - ~~(b) modulates binding of a factor involved in splicing of the NMD-exon; or~~
 - ~~(c) a combination of (a) and (b).~~
8. ~~The method of claim 7, wherein the agent interferes with binding of the factor involved in splicing of the NMD-exon.~~

- ~~9. The method of claim 7, wherein the targeted portion of the pre-mRNA is proximal to the NMD exon.~~
- ~~10. The method of claim 7, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of the 5' end of the NMD exon.~~
- ~~11. The method of claim 7, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of the 5' end of the NMD exon.~~
- ~~12. The method of claim 7, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of the 3' end of the NMD exon.~~
- ~~13. The method of claim 7, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of the 3' end of the NMD exon.~~
- ~~14. The method of claim 7, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of genomic site of GRCh38/ hg38: chr4:88031085.~~
- ~~15. The method of claim 7, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of genomic site of GRCh38/ hg38: chr4:88031085.~~
- ~~16. The method of claim 7, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600~~

~~nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site of GRCh38/ hg38: chr4:88031140.~~

- ~~17. The method of claim 7, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site of GRCh38/ hg38: chr4:88031140.~~
3. The method according to claim 1, or the composition of claim 2, wherein the target sequence of the pre-mRNA comprises a sequence with 8 contiguous nucleic acids of a sequence selected from the group consisting of premrna ENST00000237596.7, premrna ENST00000502363.1, premrna ENST00000506367.1, premrna ENST00000506727.1, premrna ENST00000508588.5, premrna ENST00000511337.5, premrna ENST00000512858.1, transcript ENST00000237596.7, transcript ENST00000502363.1, transcript ENST00000506367.1, transcript ENST00000506727.1, transcript ENST00000508588.5, transcript ENST00000511337.5, transcript ENST00000512858.1, and PKD2 5' UTR sequence (ENST00000237596.7).
4. The method according to claim 1, or the composition of claim 2, wherein the target sequence of the pre-mRNA overlaps with the NMD exon.
5. The method according to claim 1, or the composition of claim 2, wherein the target sequence of the pre-mRNA overlaps with an intron upstream or downstream of the NMD exon.
6. The method according to claim 1, or the composition of claim 2, wherein the target sequence of the pre-mRNA comprises 5' NMD exon-intron junction or 3' NMD exon-intron junction.
7. The method according to claim 1, or the composition of claim 2, wherein the target sequence of the pre-mRNA is within the NMD exon.
- ~~18.8. The method according to claim 1, or the composition of claim 2, wherein the NMD exon~~ The method of claim 7, wherein the targeted portion of the pre-mRNA is located in an intronic region between two canonical exonic regions of the pre-mRNA, and wherein the intronic region contains the NMD exon.
- ~~19. The method of claim 7, wherein the targeted portion of the pre-mRNA at least partially overlaps with the NMD exon.~~
- ~~20. The method of claim 7, wherein the targeted portion of the pre-mRNA at least partially overlaps with an intron upstream or downstream of the NMD exon.~~
- ~~21. The method of claim 7, wherein the targeted portion of the pre-mRNA comprises 5' NMD exon-intron junction or 3' NMD exon-intron junction.~~
- ~~22. The method of claim 7, wherein the targeted portion of the pre-mRNA is within the NMD exon.~~

- ~~23. The method of claim 7, wherein the targeted portion of the pre-mRNA comprises about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of the NMD exon.~~
- ~~24. The method of any one of claims 1 to 23, wherein the NMD exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in Table 3.~~
- ~~25. The method of any one of claims 1 to 23, wherein the NMD exon comprises a sequence selected from the group consisting of the sequences listed in Table 3.~~
- ~~26. The method of claim 7, wherein the pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in Table 3.~~
- ~~27. The method of claim 7, wherein the pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a sequence selected from the group consisting of the sequences listed in Table 2.~~
- ~~28. The method of claim 7, wherein the targeted portion of the pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of a sequence selected from the group consisting of the sequences listed in Table 3.~~
9. The method according to claim 1 or 3-8, or the composition according to any one of claims 2-8, wherein the pre-mRNA comprises an alternative 5' splice-site downstream of a canonical 5' splice-site, wherein a processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice-site undergoes non-sense mediated RNA decay, wherein the NMD exon comprises a cononical exon and an exon region extended by the splicing at the alternative 5' splice-site, wherein the agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice-site, thereby modulating expression of the target protein.
10. The method according to claim 1 or 3-9, or the composition according to any one of claims 2-9, wherein the processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice-site comprises a premature termination codon (PTC).
11. The method according to claim 1 or 3-10, or the composition according to any one of claims 2-10, wherein the NMD exon is defined by genomic sites GRCh38/ hg38: chr4:88031085-88031140.
12. The method according to claim 1 or 3-11, or the composition according to any one of claims 2-11, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000 nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, 60 nucleotides, 50 nucleotides upstream of genomic site of GRCh38/ hg38: chr4:88031085.
13. The method according to claim 1 or 3-12, or the composition according to any one of claims 2-12, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000

- nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, 60 nucleotides, 50 nucleotides downstream of genomic site of GRCh38/ hg38: chr4:88031085.
14. The method according to claim 1 or 3-13, or the composition according to any one of claims 2-13, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000 nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, 60 nucleotides, 50 nucleotides upstream of genomic site of GRCh38/ hg38: chr4:88031140.
15. The method according to claim 1 or 3-14, or the composition according to any one of claims 2-14, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000 nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, 60 nucleotides, 50 nucleotides downstream of genomic site of GRCh38/ hg38: chr4:88031140.
16. The method according to claim 1 or 3-15, or the composition according to any one of claims 2-15, wherein the agent is a non-sense mediated RNA decay alternative splice site (NSASS) modulating agent and the NMD exon is defined by genomic sites GRCh38/ hg38: chr4:88036354 88036480.
17. The method according to claim 1 or 3-16, or the composition according to any one of claims 2-16, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000 nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, 60 nucleotides, 50 nucleotides upstream of genomic site of GRCh38/ hg38: chr4 88036480.
18. The method according to claim 1 or 3-17, or the composition according to any one of claims 2-18, wherein the target sequence of the pre-mRNA is closer than 1500 nucleotides, 1000 nucleotides, 800 nucleotides, 700 nucleotides, 600 nucleotides, 500 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 100 nucleotides, 80 nucleotides, 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site of GRCh38/ hg38: chr4:88036480.
- 29,19. The method ~~of~~ according to claim ~~7~~,1 or 3-18, or the composition according to any one of claims 2-18, wherein the composition comprising the agent, and wherein the agent is an antisense oligomer (ASO) ~~and~~).
20. The method according to claim 1 or 3-19, or the composition according to any one of claims 2-19, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to at least 8, 9, 10, 11, 12, 13, 14, ~~15~~16, 16, 17 or 18 contiguous nucleic acids of a sequence selected from the group consisting of the sequences listed in Table 4 or Table 5 SEQ ID NOs: 1-226.
30. The method of claim 7, wherein the targeted portion of the pre-mRNA is within the non-sense mediated RNA decay inducing exon GRCh38/ hg38: chr4:88031085-88031140.

- ~~31. The method of claim 7, wherein the targeted portion of the pre-mRNA is upstream or downstream of the non-sense mediated RNA decay inducing exon GRCh38/ hg38: chr4:88031085-88031140.~~
- ~~32. The method of claim 7, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of the non-sense mediated RNA decay inducing exon GRCh38/ hg38: chr4:88031085-88031140.~~
- ~~33. The method of claim 3, wherein the polycystin 2 expressed from the processed mRNA is full-length polycystin 2 or wild-type polycystin 2.~~
- ~~34. The method of claim 3, wherein the polycystin 2 expressed from the processed mRNA is at least partially functional as compared to wild-type polycystin 2.~~
- ~~35. The method of claim 3, wherein the polycystin 2 expressed from the processed mRNA is at least partially functional as compared to full-length wild-type polycystin 2.~~
- ~~36. The method of any one of claims 1 to 35, whereby the agent modulates splicing of the NMD exon from the pre-mRNA and promotes exclusion of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA and that lacks the NMD exon.~~
- ~~37. The method of claim 36, wherein the exclusion of the NMD exon from the pre-mRNA in the cell contacted with the agent is increased by about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to exclusion of the NMD exon from the pre-mRNA in a control cell.~~
- ~~38. The method of any one of claims 1 to 37, wherein the method results in an increase in the level of the processed mRNA in the cell.~~
- ~~39. The method of claim 38, wherein the level of the processed mRNA in the cell contacted with the agent is increased by about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least~~

- about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to a level of the processed mRNA in a control cell.
40. The method of any one of claims 1 to 37, wherein the agent increases the expression of the target protein in the cell.
41. The method of claim 40, wherein a level of the target protein is increased by about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to a level of the target protein produced in a control cell.
42. The method of any one of claims 1 to 41, wherein the NMD exon comprises a premature termination codon (PTC).
43. The method of claim 2, wherein the disease or condition is associated with a loss of function mutation in the target gene or the target protein.
44. The method of claim 43, wherein the disease or condition is associated with haploinsufficiency of the target gene, and wherein the subject has a first allele encoding functional polycystin 2, and a second allele from which polycystin 2 is not produced or produced at a reduced level, or a second allele encoding nonfunctional polycystin 2 or partially functional polycystin 2.
45. The method of claim 44, wherein one or both alleles are hypomorphs or partially functional.
46. The method of claim 2 or 44, wherein the disease or condition is selected from the group consisting of: polycystic kidney disease with or without polycystic liver disease, autosomal dominant polycystic kidney disease, and intracranial aneurysm.
47. The method of claim 2 or 43, wherein the disease or condition is associated with a mutation of a *PKD1* or *PKD2* gene, wherein the subject has a first allele encoding from which:
- (i) the target protein is not produced or produced at a reduced level compared to a wild-type allele; or
 - (ii) the target protein produced is nonfunctional or partially functional compared to a wild-type allele, and
- a second allele from which:
- (iii) the target protein is produced at a reduced level compared to a wild-type allele and the target protein produced is at least partially functional compared to a wild-type allele; or
 - (iv) the target protein produced is partially functional compared to a wild-type allele.

- ~~48. The method of claim 47, wherein the disease or condition is selected from the group consisting of: polycystic kidney disease with or without polycystic liver disease, autosomal dominant polycystic kidney disease, and intracranial aneurysm.~~
- ~~49. The method of claim 47, wherein the mutation is a hypomorphic mutation.~~
- ~~50. The method of claim 47, wherein the disease or condition is associated with a mutation of a *PKD2* gene.~~
- ~~51. The method of claim 47, wherein the disease or condition is associated with a mutation of a *PKD1* gene.~~
- ~~52. The method of claim 43, wherein the agent promotes exclusion of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA and that lacks the NMD exon and increases the expression of the target protein in the cell.~~
- 53.21. The method ~~of~~according to claim 1 or 3-20, or the composition according to any one of claims 2-20, wherein the ~~agent is an antisense oligomer (ASO) and wherein the antisense oligomer~~ comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.
- 54.22. The method ~~of~~according to claim ~~11~~ or ~~2~~, ~~wherein~~3-21, or the ~~agent is an antisense oligomer (ASO) and~~composition according to any one of claims 2-21, wherein the ~~antisense oligomer~~ASO comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.
- 55.23. The method ~~of~~according to claim ~~11~~ or ~~2~~, ~~wherein~~3-22, or the ~~agent is an antisense oligomer (ASO) and~~composition according to any one of claims 2-22, wherein the ~~antisense oligomer~~ASO comprises ~~at least one~~a modified sugar moiety.
- 56.24. The method ~~of~~according to claim ~~55,1~~ or ~~3-23~~, or the composition according to any one of claims 2-23, wherein each sugar moiety of the ASO is a modified sugar moiety.
- 57.25. The method ~~of~~according to claim ~~11~~ or ~~2~~, ~~wherein~~3-24, or the ~~agent is an antisense oligomer (ASO) and~~composition according to any one of claims 2-24, wherein the ~~antisense oligomer consists of~~ASO is from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases-in length.

- ~~58.26. The method ~~of~~ according to claim ~~7~~, 1 or 3-25, or the composition according to any one of claims 2-25, wherein the ~~composition the viral vector encoding the agent is an antisense oligomer (ASO), and wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted portion of the pre-mRNA.~~ vector is a viral vector.~~
- ~~59. The method of claim 1 or 2, wherein the method comprises contacting a vector encoding the agent to the cell.~~
- ~~60. The method of claim 59, wherein the agent is a polynucleotide comprising an antisense oligomer.~~
- ~~61. The method of claim 59, wherein the vector is a viral vector.~~
- ~~62.27. The method according to claim 1 or 3-26, or the composition according to any one of claims 2-26~~61, wherein viral vector is an adenovirus-associated viral vector.
- ~~63.28. The method of claim 59; The method according to claim 1 or 3-27, or the composition according to any one of claims 2-27, wherein the agent is a polynucleotide, wherein the polynucleotide further comprises a modified snRNA.~~
- ~~64.29. The method ~~of~~ according to claim ~~63~~, 1 or 3-28, or the composition according to any one of claims 2-28, wherein the modified human snRNA is a modified U1 snRNA or a modified U7 snRNA.~~
- ~~65. The method of claim 63, wherein the modified human snRNA is a modified U7 snRNA and wherein the antisense oligomer has a sequence at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% identical to a sequence listed in Table 4 or Table 5.~~
- ~~66. The method of claim 1 or 2, wherein the method further comprises assessing processed mRNA level or expression level of the target protein.~~
30. The composition according to any one of claims 2-29, for use in therapy.
31. Use of the composition according to any one of claims 2-29, in manufacturing a medicament for treating a disease or condition in a subject in need thereof.
32. The use according to claim 31, wherein the disease or condition is associated with a deficient amount or activity of polycystin in the subject.
33. The use according to claim 31, wherein the disease or condition is associated with a loss-of-function mutation in a polycystin gene or a polycystin protein.
34. The use according to claim 31, wherein the disease or condition is associated with haploinsufficiency of a *PKD2* gene, and wherein the subject has a first allele encoding functional polycystin 2, and a second allele from which polycystin 2 is not produced, or a second allele encoding nonfunctional polycystin 2.
35. The use according to claim 31, wherein one or both alleles are hypomorphs.
36. The use according to claim 31, wherein the disease or condition is associated with a mutation of a *PKD1* or *PKD2* gene.

37. The use according to claim 36, wherein the mutation is a hypomorphic mutation.
38. The use according to [claim 31](#), wherein the disease or condition is selected from the group consisting of: polycystic kidney disease with or without polycystic liver disease, autosomal dominant polycystic kidney disease, and intracranial aneurysm.
- ~~67.39. The method of use according to claim 2,31, wherein the subject is a human.~~
- ~~68.40. The method of use according to claim 2,31, wherein the subject is a non-human animal.~~
- ~~69.41. The method of use according to claim 2,31, wherein the subject is a fetus, an embryo, or a child.~~
- ~~70.42. The method of claim 1 or 2,The use according to claim 31, wherein the cells are ex vivo.~~
- ~~71.43. The method of use according to claim 2,31, wherein the agent is to be administered by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, intravitreal, or intravenous injection of the subject.~~
- ~~72. The method of claim 2, wherein the method further comprises administering a second therapeutic agent to the subject.~~
- ~~73. The method of claim 72, wherein the second therapeutic agent is a small molecule.~~
- ~~74. The method of claim 72, wherein the second therapeutic agent is an antisense oligomer.~~
- ~~75. The method of claim 72, wherein the second therapeutic agent corrects intron retention~~
- ~~76. The method of any one of claims 1-75, wherein the method further comprises contacting a non-sense mediated RNA decay alternative splice site (NSASS) modulating agent or a viral vector encoding the agent to the cell, wherein the pre-mRNA comprises an alternative 5' splice site downstream of a canonical 5' splice site, wherein a processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice site undergoes non-sense mediated RNA decay, wherein the agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice site, thereby modulating expression of the target protein; and wherein the target gene is *PKD2*.~~
- ~~77. The method of any one of claims 1-76, wherein the method treats the disease or condition.~~
- ~~78. A composition comprising an agent or a vector encoding the agent that modulates splicing of a non-sense mediated RNA decay inducing exon (NMD-exon) from a pre-mRNA that is transcribed from a target gene and that comprises the NMD-exon, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating expression of a target protein in a cell having the pre-mRNA, wherein the target protein is encoded by a *PKD2* gene.~~
- ~~79. A composition comprising an agent or a vector encoding the agent that modulates splicing of a non-sense mediated mRNA decay inducing exon (NMD-exon) from a pre-mRNA that is transcribed from a target gene and that comprises the NMD-exon, thereby treating a disease or condition in a subject in need thereof by modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating expression of a target protein in a cell of the subject, wherein the target protein is encoded by a *PKD2* gene.~~

- ~~80. A pharmaceutical composition comprising the composition of any one of claims 78-79; and a pharmaceutically acceptable excipient and/or a delivery vehicle.~~
- ~~81. A composition comprising a non-sense mediated RNA decay alternative splice site (NSASS) modulating agent or a viral vector encoding the agent, wherein the agent modulates expression of a target protein in a cell comprising a pre-mRNA that is transcribed from a target gene and encodes the target protein, wherein the pre-mRNA comprises an alternative 5' splice-site downstream of a canonical 5' splice-site, wherein a processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice-site undergoes non-sense mediated RNA decay, wherein the agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice-site; and wherein the target gene is *PKD2*.~~
- ~~82. The composition of claim 81, wherein the agent modulates processing of the pre-mRNA by preventing or decreasing splicing at the alternative 5' splice-site.~~
- ~~83. The composition of claim 81 or 82, wherein the agent modulates processing of the pre-mRNA by promoting or increasing splicing at the canonical 5' splice-site.~~
- ~~84. The composition of claim 81, wherein modulating the splicing of the pre-mRNA at the alternative 5' splice-site increases the expression of the target protein in the cell.~~
- ~~85. The composition of any one of claims 81-84, wherein the processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice-site comprises a premature termination codon (PTC).~~
- ~~86. The composition of any one of claims 81-85, wherein the agent is a small molecule.~~
- ~~87. The composition of any one of claims 81-85, wherein the agent is a polypeptide.~~
- ~~88. The composition of claim 87, wherein the polypeptide is a nucleic acid binding protein.~~
- ~~89. The composition of claim 88, wherein the nucleic acid binding protein contains a TAL-effector or zinc finger binding domain.~~
- ~~90. The composition of claim 88, wherein the nucleic acid binding protein is a Cas family protein.~~
- ~~91. The composition of claim 88, wherein the polypeptide is accompanied by or complexed with one or more nucleic acid molecules.~~
- ~~92. The composition of any one of claims 81-85, wherein the agent is an antisense oligomer (ASO) complementary to the targeted region of the pre-mRNA.~~
- ~~93. The composition of claim 92, wherein the agent is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted region of the pre-mRNA encoding the target protein.~~
- ~~94. The composition of claim 92 or 93, wherein the agent comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.~~
- ~~95. The composition of any one of claims 92-94, wherein the agent comprises a phosphorodiamidate morpholino.~~
- ~~96. The composition of any one of claims 92-95, wherein the agent comprises a locked nucleic acid.~~
- ~~97. The composition of any one of claims 92-96, wherein the agent comprises a peptide nucleic acid.~~

- ~~98. The composition of any one of claims 92-96, wherein the agent comprises a 2'-O-methyl.~~
- ~~99. The composition of any one of claims 92-98, wherein the agent comprises a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.~~
- ~~100. The composition of any one of claims 92-99, wherein the agent comprises at least one modified sugar moiety.~~
- ~~101. The composition of claim 100, wherein each sugar moiety is a modified sugar moiety.~~
- ~~102. The composition of any one of claims 81-85 or 92-101, wherein the agent is an antisense oligomer, and wherein the agent consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.~~
- ~~103. The composition of any one of claims 78, 79 and 81, wherein the composition comprises a vector encoding the agent.~~
- ~~104. The method of claim 103, wherein the agent is a polynucleotide comprising an antisense oligomer.~~
- ~~105. The method of claim 103, wherein the vector is a viral vector.~~
- ~~106. The composition of claim 105, wherein viral vector is an adenovirus-associated viral vector.~~
- ~~107. The composition of claim 103, wherein the polynucleotide further comprises a modified snRNA.~~
- ~~108. The composition of claim 107, wherein the modified human snRNA is a modified U1 snRNA or a modified U7 snRNA.~~
- ~~109. The composition of claim 107, wherein the modified human snRNA is a modified U7 snRNA and wherein the antisense oligomer has a sequence at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% identical to a sequence listed in Table 4 or Table 5.~~
- ~~110. A composition comprising a nucleic acid molecule that encodes for the agent according to the composition of any one of claims 81-85 or 87-109.~~
- ~~111. The composition of claim 110, wherein the nucleic acid molecule is incorporated into a viral delivery system.~~
- ~~112. The composition of claim 111, wherein the viral delivery system is an adenovirus-associated vector.~~
- ~~113. The composition of claim 81, wherein the viral vector is an adenovirus-associated viral vector.~~
- ~~114. A method of modulating expression of a target protein in a cell comprising a pre-mRNA that is transcribed from a target gene and encodes the target protein, the method comprising contacting~~

a non-sense mediated RNA decay alternative splice site (NSASS) modulating agent or a viral vector encoding the agent to the cell, wherein the pre-mRNA comprises an alternative 5' splice-site downstream of a canonical 5' splice-site, wherein a processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice-site undergoes non-sense mediated RNA decay, wherein the agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice-site, thereby modulating expression of the target protein; and wherein the target gene is *PKD2*.

115. The method of claim 114, wherein the agent:

- (a) binds to a targeted portion of the pre-mRNA;
- (b) modulates binding of a factor involved in splicing at the alternative 5' splice-site; or
- (c) a combination of (a) and (b).

116. The method of claim 115, wherein the agent interferes with binding of the factor involved in splicing at the alternative 5' splice-site to a region of the targeted portion.

117. The method of any one of claims 115-116, wherein the targeted portion of the pre-mRNA is proximal to the alternative 5' splice-site.

118. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of the alternative 5' splice-site.

119. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of the alternative 5' splice-site.

120. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of the alternative 5' splice-site.

121. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30

- nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of the alternative 5' splice site.
122. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of genomic site of GRCh38/hg38: chr4:88036480.
123. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of genomic site of GRCh38/hg38: chr4:88036480.
124. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of genomic site of GRCh38/hg38: chr4:88036480.
125. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is at least about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of genomic site of GRCh38/hg38: chr4:88036480.
126. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is located in a region between the canonical 5' splice site and the alternative 5' splice site.
127. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is located in an exon region extended by the splicing at the alternative 5' splice site.
128. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA at least partially overlaps with the alternative 5' splice site.
129. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA at least partially overlaps with a region upstream or downstream of the alternative 5' splice site.

130. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is within an exon region extended by the splicing at the alternative 5' splice site.
131. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA comprises about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more consecutive nucleotides of an exon region extended by the splicing at the alternative 5' splice site.
132. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is located in an intronic region between two canonical exons.
133. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is located in one of the two canonical exons.
134. The method of any one of claims 115-117, wherein the targeted portion of the pre-mRNA is located in a region spanning both an intron and a canonical exon.
135. The method of claim 114, wherein the level the target protein in the cell is increased about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to the level of processed mRNA encoding the target protein in a control cell.
136. The method of any one of claims 114-135, wherein modulation of splicing of the pre-mRNA increases production of the processed mRNA encoding the target protein.
137. The method of claim 136, wherein the level of processed mRNA encoding the target protein in the cell contacted with the agent is increased about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to the level of processed mRNA encoding the target protein in a control cell.
138. The method of any one of claims 114-137, wherein the target protein is the canonical isoform of the protein.

139. The method of any one of claims 114-138, wherein the processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice site comprises a premature termination codon (PTC).
140. The method of any one of claims 114-139, wherein the method further comprises contacting a second agent or a vector encoding the second agent to the cell, wherein the pre-mRNA comprises a non-sense mediated RNA decay inducing exon (NMD-exon), whereby the second agent modulates splicing of the NMD-exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating the expression of the target protein in the cell, wherein the target protein is encoded by a *PKD2* gene.
141. The method of any one of claims 114-140, wherein the NSASS-modulating agent is the composition of any one of claims 81-113.
142. A pharmaceutical composition comprising the composition of any one of claims 81-113; and a pharmaceutically acceptable excipient and/or a delivery vehicle.
143. A method of treating or reducing the likelihood of developing a disease or condition in a subject in need thereof, the method comprising: administering to the subject a pharmaceutical composition to a subject in need thereof, wherein the pharmaceutical composition comprises a composition comprising a non-sense mediated RNA decay alternative splice site (NSASS) modulating agent or a viral vector encoding the agent, wherein the agent modulates expression of a target protein in a cell comprising a pre-mRNA that is transcribed from a target gene and encodes the target protein; wherein the pre-mRNA comprises an alternative 5' splice site downstream of a canonical 5' splice site, wherein splicing of the pre-mRNA at the alternative 5' splice site leads to non-sense mediated RNA decay of the alternatively spliced mRNA, wherein the agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice site; and wherein the target gene is *PKD2*; and a pharmaceutically acceptable excipient.
144. A method of treating or reducing the likelihood of developing a disease or condition in a subject in need thereof, the method comprising: administering to the subject the pharmaceutical composition of claim 81.
145. The method of any one of claims 143-144, wherein the disease is polycystic kidney disease with or without polycystic liver disease, autosomal dominant polycystic kidney disease, or intracranial aneurysm.
146. The method of any one of claims 143-144, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin-2.
147. The method of any one of claims 143-144, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin-1.
148. The method of any one of claims 143-144, wherein the disease or condition is a disease or condition associated with a deficiency in amount or activity of a protein that polycystin-2 functionally augments, compensates for, replaces or functionally interacts with.

- ~~149. The method of any one of claims 143-148, wherein the disease or the condition is caused by a deficient amount or activity of the target protein.~~
- ~~150. The method of any one of claims 143-149, wherein the agent increases the level of the processed mRNA encoding the target protein in the cell.~~
- ~~151. The method of claim 150, wherein the level of processed mRNA encoding the target protein in the cell contacted with the agent is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell.~~
- ~~152. The method of any one of claims 143-151, wherein the agent increases the expression of the target protein in the cell.~~
- ~~153. The method of claim 152, wherein the level the target protein in the cell is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell.~~
- ~~154. The method of any one of claims 143-153, wherein the method further comprises assessing mRNA levels or expression levels of the target protein.~~
- ~~155. The method of any one of claims 143-154, wherein the method further comprises assessing the subject's genome for at least one genetic mutation associated with the disease.~~
- ~~156. The method of claim 155, wherein at least one genetic mutation is within a locus of a gene associated with the disease.~~
- ~~157. The method of claim 155, wherein at least one genetic mutation is within a locus associated with expression of a gene associated with the disease.~~
- ~~158. The method of claim 155, wherein at least one genetic mutation is within the *PKD2* gene locus.~~
- ~~159. The method of claim 155, wherein at least one genetic mutation is within the *PKD1* gene locus.~~

- ~~160. The method of claim 155, wherein at least one genetic mutation is within a locus associated with *PKD2* gene expression.~~
- ~~161. The method of any one of claims 143-160, wherein the subject is a human.~~
- ~~162. The method of any one of claims 143-160, wherein the subject is a non-human animal.~~
- ~~163. The method of any one of claims 143-160, wherein the subject is a fetus, an embryo, or a child.~~
- ~~164. The method of any one of claims 143-163, wherein the cell or the cells is *ex vivo*, or in a tissue, or organ *ex vivo*.~~
- ~~165. The method of any one of claims 143-164, wherein the agent is administered to the subject by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.~~
- ~~166. The method of any one of claims 143-165, wherein the method treats the disease or condition.~~
- ~~167. A therapeutic agent for use in the method of any one of claims 143-166.~~
- ~~168. A pharmaceutical composition comprising the therapeutic agent of claim 167 and a pharmaceutically acceptable excipient.~~
- ~~169. A method of treating or reducing the likelihood of developing a disease or condition in a subject in need thereof, comprising administering the pharmaceutical composition of claim 168 by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection to the subject.~~
- ~~170. The method of claim 169, wherein the method treats the subject.~~
- ~~171. A method of increasing expression of a target protein in a cell having a processed mRNA that encodes the target protein, the method comprising delivering into the cell: (1) a first agent or a first nucleic acid sequence encoding the first agent, and (2) a second agent or a second nucleic acid sequence encoding the second agent, wherein the pre-mRNA comprises a non-sense mediated RNA decay inducing exon (NMD exon), whereby the first agent modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating the expression of the target protein in the cell; and wherein the pre-mRNA comprises an alternative 5' splice site downstream of a canonical 5' splice site, wherein a processed mRNA that is produced by splicing of the pre-mRNA at the alternative 5' splice site undergoes non-sense mediated RNA decay, wherein the second agent modulates processing of the pre-mRNA by modulating splicing at the alternative 5' splice site, thereby modulating expression of the target protein; wherein the target protein is encoded by a *PKD2* gene.~~

- ~~172. A composition comprising an agent or a vector encoding the agent, wherein the agent comprises an antisense oligomer with at least 80% sequence identity to a sequence selected from the group consisting of a sequence of Table 4 or Table 5.~~
- ~~173. A composition comprising a vector encoding an agent, wherein the agent comprises a polynucleic acid comprising a sequence with at least 80% sequence identity to a sequence selected from the group consisting sequence of Table 4 or Table 5.~~
- ~~174. A method of increasing expression of a polycystin 2 protein in a cell having a processed mRNA that encodes the polycystin 2 protein and that comprises a translation regulatory element that inhibits translation of the processed mRNA, the method comprising contacting an agent or a vector encoding the agent to the cell, wherein the agent modulates a structure of the translation regulatory element, thereby increasing expression of the polycystin 2 protein in the cell.~~
- ~~175. A method of increasing expression of a polycystin 2 protein in a cell having a processed mRNA that encodes the polycystin 2 protein and that comprises a translation regulatory element that inhibits translation of the processed mRNA, the method comprising contacting an agent or a vector encoding the agent to the cell, wherein the agent (a) binds to a targeted portion of the processed mRNA; (b) modulates interaction of the translation regulatory element with a factor involved in translation of the processed mRNA; or (c) a combination of (a) and (b), thereby increasing expression of the polycystin 2 protein in the cell.~~
- ~~176. A method of modulating expression of an polycystin 2 protein in a cell, the method comprising contacting an agent or a vector encoding the agent to the cell, wherein the agent comprises an antisense oligomer with at least 80% sequence identity to a sequence selected from the group consisting of a sequence of Table 4 or Table 5.~~
- ~~177. A composition comprising an agent, wherein the agent comprises an antisense oligomer that binds to a targeted portion of a processed mRNA that encodes polycystin 2 protein, wherein the targeted portion of the processed mRNA comprises at least one nucleotide of the main start codon of the processed mRNA or is within the 5' UTR of the processed mRNA.~~
- ~~178. A composition comprising a vector encoding an agent, wherein the agent comprises a polynucleic acid comprising a sequence that binds to a targeted portion of a processed mRNA that encodes polycystin 2 protein, wherein the targeted portion of the processed mRNA comprises at least one nucleotide of the main start codon of the processed mRNA or is within the 5' UTR of the processed mRNA.~~
- ~~179. A composition comprising an agent, wherein the agent modulates structure of a translation regulatory element of a processed mRNA that encodes an polycystin 2 protein, thereby increasing expression of the polycystin 2 protein, and wherein the translation regulatory element inhibits translation of the processed mRNA.~~
- ~~180. A composition comprising a vector encoding an agent, wherein the agent modulates structure of a translation regulatory element of a processed mRNA that encodes an polycystin 2 protein,~~

thereby increasing expression of the polycystin 2 protein, and wherein the translation regulatory element inhibits translation of the processed mRNA.

181. A composition comprising an agent, wherein the agent increases translation of a processed mRNA in a cell, wherein the processed mRNA encodes polycystin 2 protein and comprises a translation regulatory element that inhibits the translation of the processed mRNA, wherein the agent modulates a structure of the translation regulatory element, thereby increasing translation efficiency and/or the rate of translation of the processed mRNA, wherein the agent (a) binds to a targeted portion of the processed mRNA; (b) modulates interaction of the translation regulatory element with a factor involved in translation of the processed mRNA; or (c) a combination of (a) and (b).
182. A composition comprising a vector encoding an agent, wherein the agent increases translation of a processed mRNA in a cell, wherein the processed mRNA encodes polycystin 2 protein and comprises a translation regulatory element that inhibits the translation of the processed mRNA, wherein the agent modulates a structure of the translation regulatory element, thereby increasing translation efficiency and/or the rate of translation of the processed mRNA, wherein the agent (a) binds to a targeted portion of the processed mRNA; (b) modulates interaction of the translation regulatory element with a factor involved in translation of the processed mRNA; or (c) a combination of (a) and (b).
183. A method of increasing expression of a target protein in a cell having a processed mRNA that encodes the target protein and comprises a translation regulatory element that inhibits translation of the processed mRNA, the method comprising delivering into the cell: (1) a first agent or a first nucleic acid sequence encoding the first agent, and (2) a second agent or a second nucleic acid sequence encoding the second agent, wherein the first agent modulates splicing of a pre-mRNA that is transcribed from a target gene that encodes the target protein, and wherein the second agent modulates a structure of the translation regulatory element of the processed mRNA that encodes the target protein, thereby increasing the expression of the target protein in the cell, wherein the target protein is polycystin 2.
184. A method of increasing expression of a target protein in a cell having a processed mRNA that encodes the target protein and comprises a translation regulatory element that inhibits translation of the processed mRNA, the method comprising delivering into the cell: (1) a first agent or a first nucleic acid sequence encoding the first agent, and (2) a second agent or a second nucleic acid sequence encoding the second agent, wherein the first agent modulates splicing of a pre-mRNA that is transcribed from a target gene that encodes the target protein, and wherein the second agent (a) binds to a targeted portion of the processed mRNA; (b) modulates interaction of the translation regulatory element with a factor involved in translation of the processed mRNA; or (c) a combination of (a) and (b), thereby increasing the expression of the target protein in the cell, wherein the target protein is polycystin 2.