



# Awareness of Nucleic Acid-Based Therapies

An InCrowd Syndicated Report

October 16, 2019

# Research Purpose

## Survey Goals:

- (1) Provide a baseline understanding of current knowledge among physicians regarding the types of nucleic acid-based therapies, their mechanisms of action, and their current and future promise.
- (2) Serve as a vehicle for future surveys to assess how knowledge and perceptions change over time.



# Methodology

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METHOD 12-Minute MicroSurvey  
4 Questions

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CROWDS PCPs, Oncologists, &  
Pediatricians

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SAMPLE SIZE n=250

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FIELDING PERIOD September 8-10, 2019

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**This report explores physician awareness of the following RNA- or DNA-based therapeutic methods:**

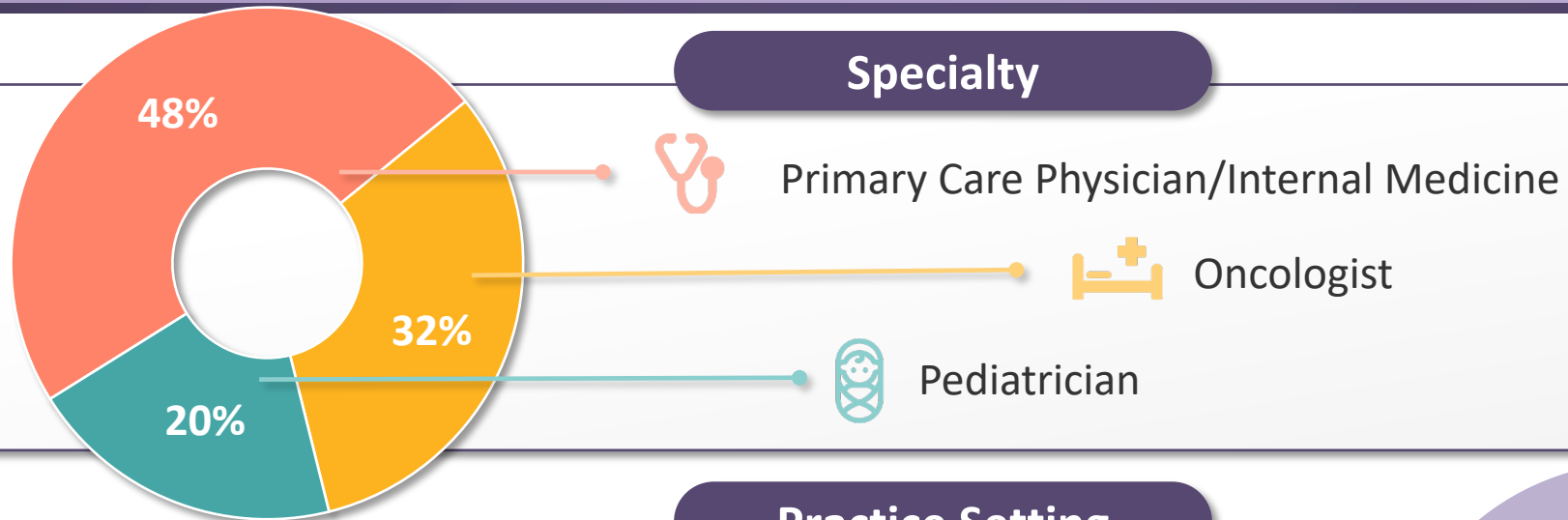
- RNAi (RNA interference)
- siRNA (short interfering RNAs)
- ASO (antisense oligonucleotides)
- mRNA (messenger ribonucleic acid)
- AAV (adeno-associated virus)
- **CRISPR** (clustered regularly interspaced short palindromic repeats)
- **TALENs** (transcription activator-like effector nuclease)



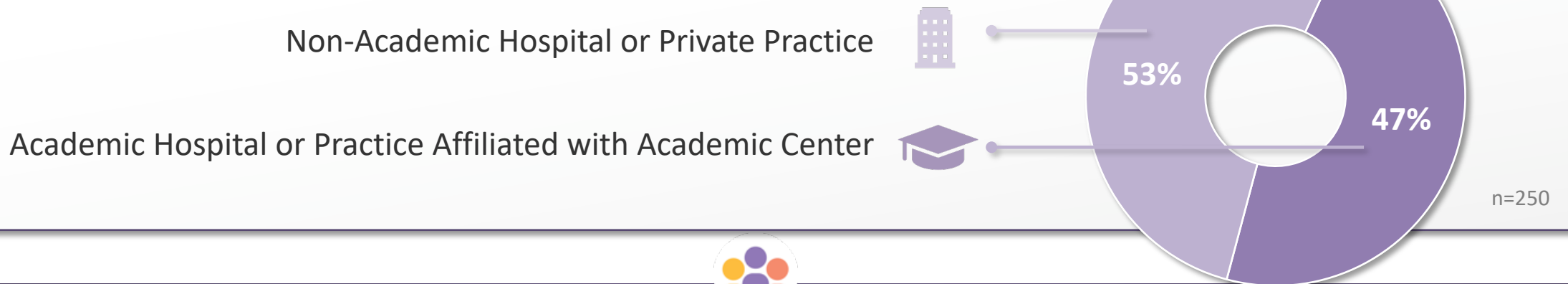
# Respondent Demographics

Respondents are PCPs (48%), oncologists (32%), and pediatricians (20%), with a near equal split between those in academically associated (47%) and non-associated (53%) practices.

## Specialty



## Practice Setting





# Executive Summary



**Only 56% of screened respondents report at least being somewhat familiar** with RNA- or DNA-based therapeutic methods. Only 7% report high familiarity. Oncologists had the highest familiarity of the specialists surveyed.



**Among RNA/DNA terms, the most identifiable are mRNA and CRISPR.** Less than half are familiar with AAV, siRNA, RNAi, and ASO, and less than a quarter are familiar with TALENS. Oncologists tend to have the highest familiarity across terms compared to PCPs and Pediatricians. Misunderstanding is common.



**CRISPR, TALENS, and AAV are most commonly considered 'gene therapies.'** But about half associate the term with RNAi, siRNA, ASO, and mRNA. Lack of knowledge is pervasive.



**Roughly 1/3 to 2/3 of respondents understand basic uses for nucleic acid-based therapies,** like use of CRISPR for permanent DNA edits, and use of mRNA and AAV for the creation of vaccine vectors. Few however have insight into the types of products currently on the market, with over half believing that there are currently no FDA-approved therapies.



**83% of respondents are unaware of any approved nucleic acid-based therapies.** Among those who are, Alnylam's Onpattro for amyloidosis and Novartis' Zolgensma for SMA are the most frequently mentioned. Great opportunity for education of approved therapies.



**Respondents overwhelmingly choose CRISPR as the most promising nucleic acid-based therapy,** citing the fact that it directly addresses the root cause of disease progression by targeting DNA.



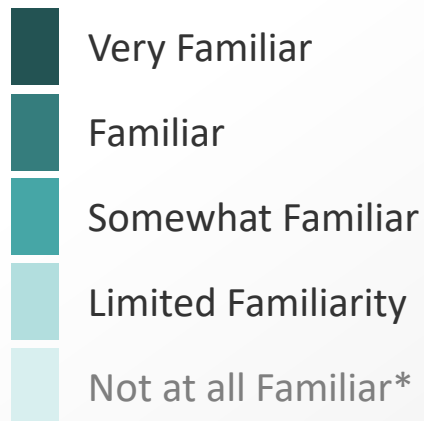
# Familiarity with Nucleic Acid-Based Therapy BY SPECIALTY

Oncologists report substantially higher familiarity with nucleic-based therapy, with 52% reporting high levels of familiarity compared to just 20% of PCPs and 15% of pediatricians

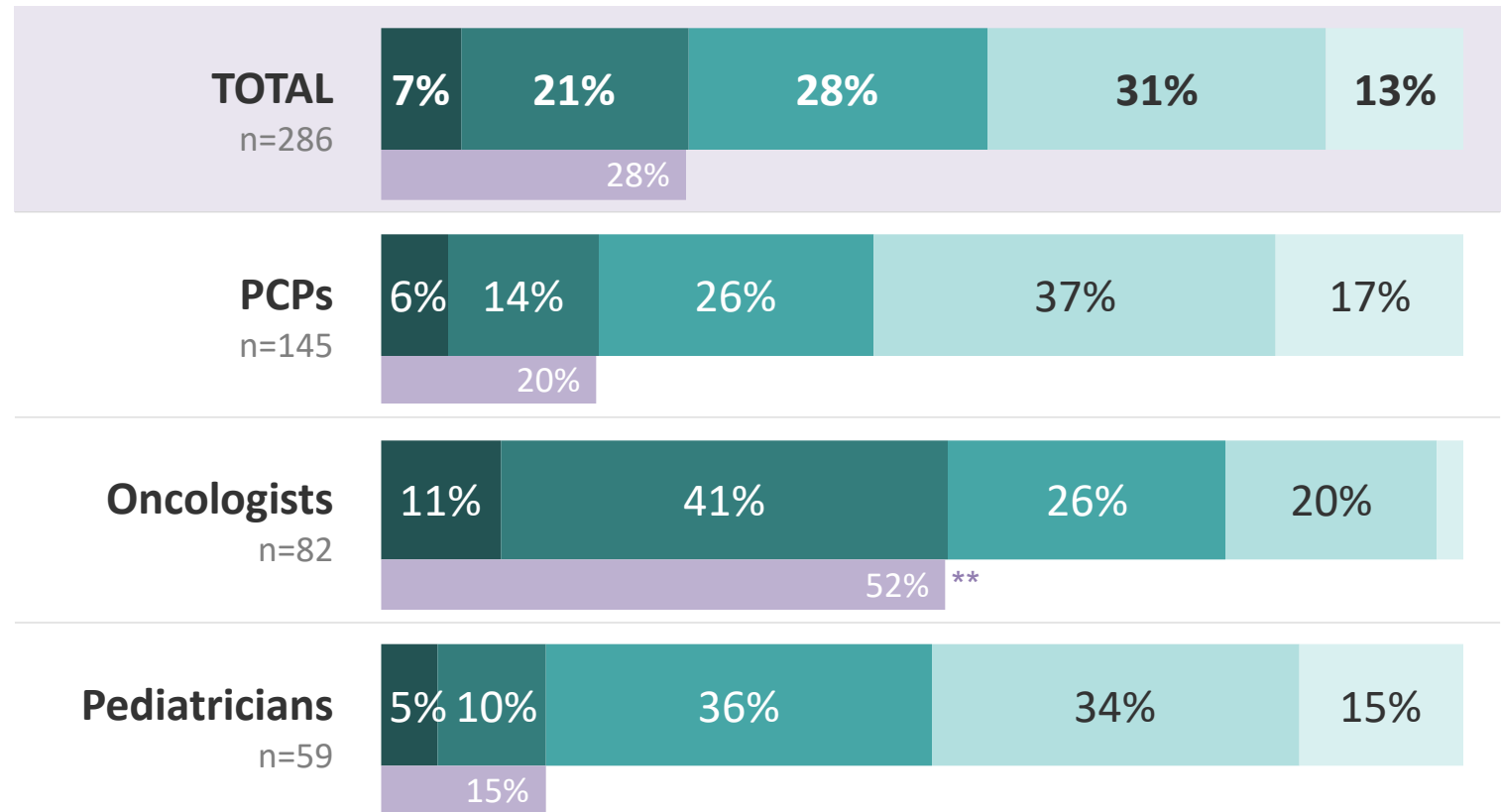
## S1

How familiar are you with RNA- or DNA-based therapeutic methods?

## KEY



\*Screened out of remaining survey questions



\*\* Difference in proportion statistically significant at the 95% CI



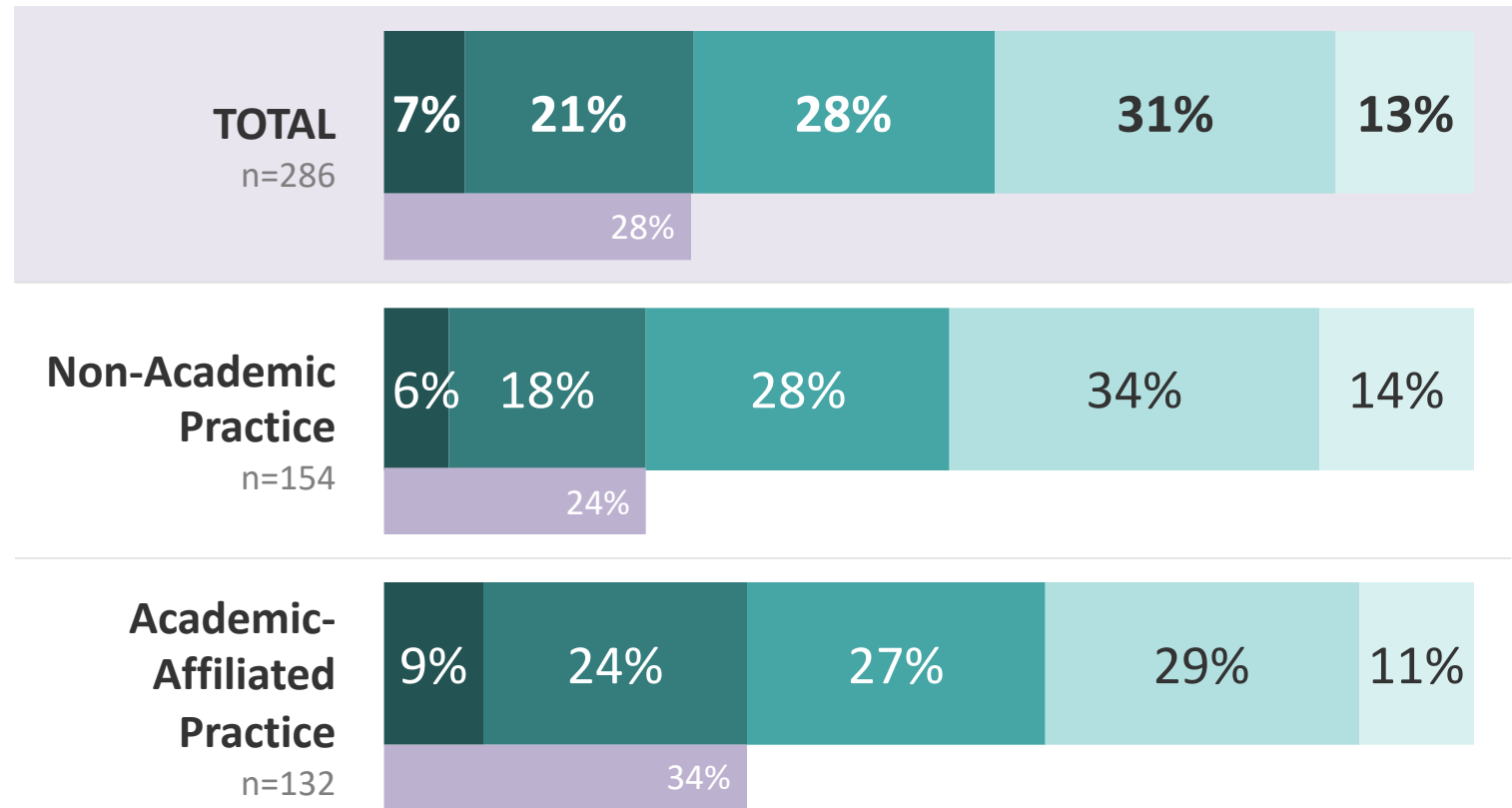
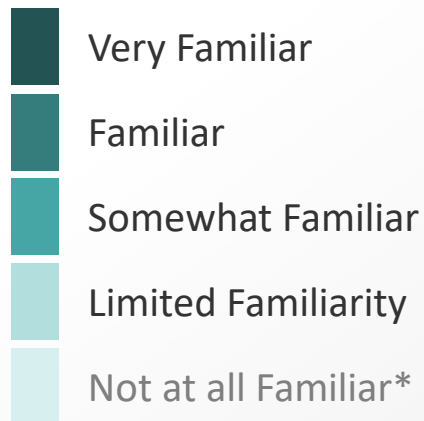
# Familiarity with Nucleic Acid-Based Therapy BY PRACTICE SETTING

Physicians in academic practices report slightly higher familiarity, with 34% reporting high levels of familiarity compared to 24% in non-academic community practices.

## S1

How familiar are you with RNA- or DNA-based therapeutic methods?

## KEY



\*Screened out of remaining survey questions

\*\* No statistical significance at the 95% CI



# Familiarity with Different Related Terms BY SPECIALTY

Among RNA/DNA terms, the most identifiable are mRNA (92%) and CRISPR (64%). Oncologists have the most comprehensive familiarity, with over 20% higher familiarity of most terms compared to other specialties. Academic based physicians report higher levels of awareness across many terms.\*

## Q1

Which of the following terms are familiar to you?

Related Terms	Total n=250	PCP n=120	Onc n=80	Ped n=50
<b>mRNA</b> messenger RNA	92%	90%	93%	96%
<b>CRISPR</b> clustered regularly interspaced short palindromic repeats	64%	53%	88%	54%
<b>AAV</b> adeno-associated virus	44%	35%	60%	42%
<b>siRNA</b> short interfering RNAs	39%	34%	56%	24%
<b>RNAi</b> RNA interference	38%	41%	46%	20%
<b>ASO</b> antisense oligonucleotides	36%	28%	53%	30%
<b>TALENS</b> transcription activator-like effector nuclease	19%	22%	21%	8%



# Approaches Considered 'Gene Therapy'

CRISPR, TALENS, and AAV are most commonly considered 'gene therapies.' About half associate this term with RNAi, siRNA, ASO, and mRNA. Oncologists and physicians in academic centers are most likely to identify appropriate terms that are 'gene therapies'. Misunderstanding is quite common.\*\*

## Q2

Of these approaches, which, if any, do you consider gene therapies?\*

\* Among those familiar with therapeutic approach

Therapeutic Approach	% Considering 'Gene Therapy'	n-size # familiar
<b>CRISPR</b> clustered regularly interspaced short palindromic repeats	92%	160
<b>TALENS</b> transcription activator-like effector nuclease	72%	47
<b>AAV</b> adeno-associated virus	67%	111
<b>RNAi</b> RNA interference	54%	96
<b>siRNA</b> short interfering RNAs	53%	98
<b>ASO</b> antisense oligonucleotides	51%	90
<b>mRNA</b> messenger RNA	48%	230



# Therapeutic Approach Top Associations

Roughly 1/3 to 2/3 of respondents understand basic uses for nucleic acid-based therapies, however few have insight into the products currently on the market.\*

## Q3a

Select the term(s) that best answers each of the statements provided below.



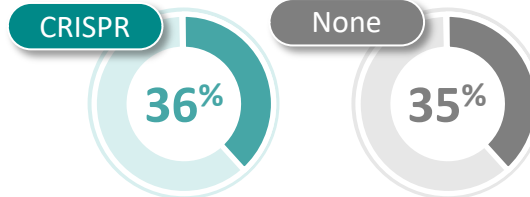
Involves **intentional and permanent changes** at the **DNA level**



- ✓ CRISPR is being used to edit patient DNA with conditions such as cancer, sickle cell disease, and other hereditary illnesses.
- ✗ TALENs and some AAVs are also being used to edit a patient's genome.



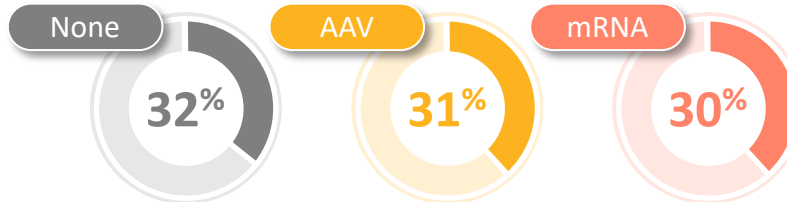
May cause **unintended permanent changes** at the **DNA level**



- ✓✗ Therapies that work at the DNA level (CRISPR, TALENs, AAVs) risk potential unwanted changes to the genome.



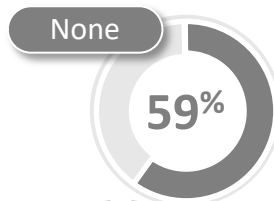
Can be used to make **vaccines**



- ✗✓✓ AAV and mRNA vaccines are currently under development to treat infectious diseases and cancer.



Has already yielded **FDA-approved medicines**



- ✗ There are several marketed nucleic acid-based therapies with FDA approvals for AAVs, ASOs, and one siRNA/RNAi. CRISPR, mRNA, CRISPR and TALENs are still in early phase clinical trials.

n=250





# Knowledge of Approved Medications

The vast majority, 83%, of respondents are unaware of any approved nucleic acid-based therapies. Among those who are aware, Alnylam's Onpattro for amyloidosis and Novartis' Zolgensma for SMA are most frequently mentioned.\*

## Q3b

Please list any FDA-approved medications based on the above approaches that you're aware of.

Approved Therapy	Company	Indications	Class	% Mentioning
<b>ONPATTRO</b> patisiran	Alnylam	hATTR amyloidosis	RNAi/ siRNA	<b>3.6%</b>
<b>ZOLGENSMA</b> onasemnogene abeparvovec	Avexis, Novartis	Spinal muscular atrophy (SMA)	AAV	<b>2.4%</b>
<b>CAR-T (Unspecified)</b>	-	Leukemia, Lymphoma	Other	<b>2.4%</b>
<b>LUXTURNA</b> voretigene neparvovec	Spark	Retinal disease	AAV	<b>1.6%</b>
<b>SPINRAZA</b> nusinersen	Biogen	Spinal muscular atrophy (SMA)	ASO	<b>0.8%</b>
<b>VITRAVENE</b> Fomivirsen	ISIS	Cytomegalovirus retinitis	ASO	<b>0.8%</b>
<b>IMLYGIC</b> talimogene laherparepvec, 'T-VEC'	AMGEN	Melanoma	Other	<b>0.8%</b>
<b>TEGSEDI</b> inotersen	Akcea, Ionis	hATTR amyloidosis	ASO	<b>0.4%</b>
<b>KYNAMRO</b> mipomersen sodium	Genzyme	Homozygous familial hypercholesterolemia	ASO	<b>0.4%</b>
<b>EXONDYS 51</b> eteplirsen	Sarepta	Duchenne muscular dystrophy	ASO	<b>0.4%</b>
<b>Don't Know</b>	-	-	-	<b>83%</b>
<b>Misidentified Therapy</b>	-	-	-	<b>5.2%</b>

n=250



# Most Promising Therapy

Respondents, particularly oncologists, overwhelmingly choose CRISPR as the most promising nucleic acid-based therapy, citing the fact that it directly addresses the root cause of disease progression by targeting DNA. Practice setting does not impact results.\*

## Q4

Please identify which one of the following approaches you believe holds the most promise for improving the lives of your patients. Please explain your choice.

Therapeutic Approach	Total n=250	Familiar with All n=19	Reasoning Select Open End Verbatim
<b>CRISPR</b> clustered regularly interspaced short palindromic repeats	28%	53%	<i>"Most direct and specific way to modify genes that are the basis of disease."</i>
<b>mRNA</b> messenger RNA	9%	11%	<i>"Treats at the initial molecular level, highly funded and well studied."</i>
<b>AAV</b> adeno-associated virus	3%	11%	<i>"Promising data, less potential for long term negative impact"</i>
<b>RNAi</b> RNA interference	3%	0%	<i>"Possibility to alter protein metabolism"</i>
<b>ASO</b> antisense oligonucleotides	2%	11%	<i>"Already approved parent therapeutic agents"</i>
<b>siRNA</b> short interfering RNAs	2%	5%	<i>"Most intriguing mechanistically in oncology"</i>
<b>TALENS</b> transcription activator-like effector nuclease	1%	0%	<i>"Good scientific rationale"</i>
<b>Unsure</b>	50%	11%	<i>"Too little clinical data"</i>

n=250



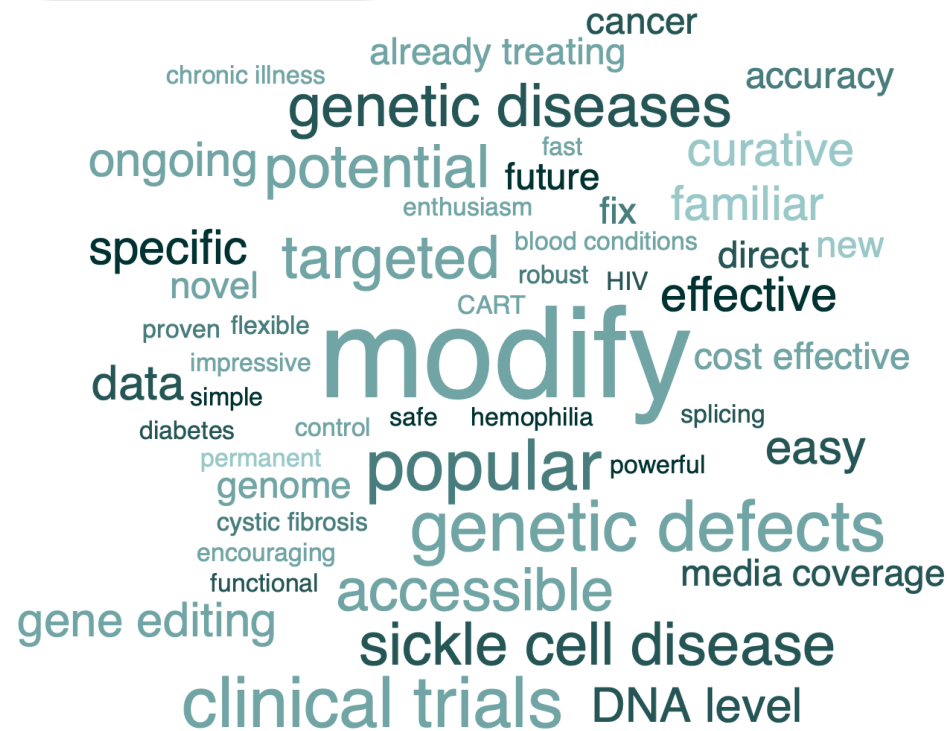
# Most Promising Therapy

Those who find CRISPR to be the most promising therapy mention its popularity, ability to modify specific genetic defects, potential in treating genetic diseases and sickle cell disease, and success in clinical trials. Those who choose mRNA mention high familiarity with the treatment, often because it has been well studied to date.

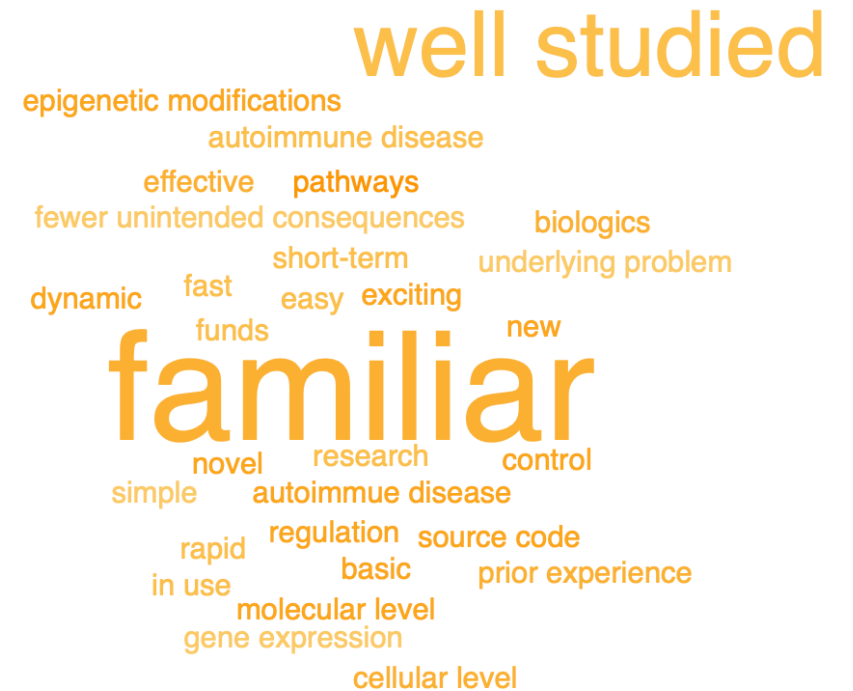
## Q4

Please identify which one of the following approaches you believe holds the most promise for improving the lives of your patients. Please explain your choice.

## CRISPR n=71



## mRNA n=23



# Most Promising Therapy

Those who choose AAV as most promising mention success of gene transfer and opportunities in hemophilia, and those who choose RNAi mention potential to alter protein metabolism without making permanent changes.

## Q4

Please identify which one of the following approaches you believe holds the most promise for improving the lives of your patients. Please explain your choice.

### AAV n=9

vector based  
vaccines  
specific encouraging hemophilia  
gene transfer  
long term safety FDA approved  
data mechanism of action  
new

### siRNA n=6

groundbreaking  
solid tumors target gene  
articles intriguing  
hemological malignancies  
mechanistically  
break up DNA  
modify new class

### RNAi n=8

gene expression  
genetic diseases not permanent cancer  
data clinical trials  
future alter protein metabolism  
vaccines advanced

### ASO n=5

FDA approved  
favorable experience  
BCL data  
medical advances



# Identified Knowledge Gaps and Key Takeaways

There is significant confusion among prescribers regarding several aspects of nucleic acid-based therapies, including:

- A misunderstanding of therapies that involve changes to DNA
- Lack of an understanding of DNA-level risks
- Widespread confusion regarding current FDA approved therapies





# APPENDIX

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# Familiarity with Different Related Terms BY SPECIALTY

Oncologists have the most comprehensive familiarity across DNA/RNA therapy terms, with over 20% higher familiarity of CRISPR, AAV, siRNA, RNAi, ASO, and TALENs compared to other specialties.

## Q1

Which of the following terms are familiar to you?

Related Terms	Total n=250	PCP n=120	Onc n=80	Ped n=50
<b>mRNA</b> messenger RNA	92%	90%	93%	96%
<b>CRISPR</b> clustered regularly interspaced short palindromic repeats	64%	53%	88%*	54%
<b>AAV</b> adeno-associated virus	44%	35%	60%*	42%
<b>siRNA</b> short interfering RNAs	39%	34%	56%*	24%
<b>RNAi</b> RNA interference	38%	41%	46%	20%*
<b>ASO</b> antisense oligonucleotides	36%	28%	53%*	30%
<b>TALENS</b> transcription activator-like effector nuclease	19%	22%	21%	8%*

\* Difference in proportion statistically significant at the 95% CI



# Familiarity with Different Related Terms BY PRACTICE SETTING

Physicians in academic practice report higher levels of awareness across nearly all therapies, with over 10% higher familiarity of CRISPR, siRNA, RNAi, ASO, and TALENs compared to other practice settings.

## Q1

Which of the following terms are familiar to you?

Related Terms	Total <small>n=250</small>	Non-Academic <small>n=132</small>	Academic <small>n=118</small>
<b>mRNA</b> messenger RNA	92%	92%	92%
<b>CRISPR</b> clustered regularly interspaced short palindromic repeats	64%	58%*	70%*
<b>AAV</b> adeno-associated virus	44%	46%	42%
<b>siRNA</b> short interfering RNAs	39%	31%*	48%*
<b>RNAi</b> RNA interference	38%	32%*	46%*
<b>ASO</b> antisense oligonucleotides	36%	30%*	43%*
<b>TALENS</b> transcription activator-like effector nuclease	19%	15%	23%

\* Difference in proportions statistically significant at the 95% CI



# Approaches Considered 'Gene Therapy' BY SPECIALTY

Nearly all physician types consider CRISPR a gene therapy and over three quarters of oncologists and pediatricians also consider TALENs a gene therapy.

## Q2

Of these approaches, which, if any, do you consider gene therapies?\*

\* Among those familiar with therapeutic approach

Therapeutic Approach	Total n = 47-230	PCP n = 26-108	Onc n = 17-74	Ped n = 4-48
<b>CRISPR</b> clustered short palindromic repeats	92 %	89 %	94 %	93 %
<b>TALENS</b> transcription activator-like effector nuclease	72 %	69 %	76 %	75 %
<b>AAV</b> adeno-associated virus	67 %	50 %	85 %	57 %
<b>RNAi</b> RNA interference	54 %	67 %	38 %	50 %
<b>siRNA</b> short interfering RNAs	53 %	66 %	36 %	75 %
<b>ASO</b> antisense oligonucleotides	51 %	61 %	45 %	47 %
<b>mRNA</b> messenger RNA	48 %	57 %	34 %	50 %



# Approaches Considered 'Gene Therapy' BY PRACTICE SETTING

Around three quarters of physicians in academic centers consider TALENs and AAV therapy to be gene therapies.

## Q2

Of these approaches, which, if any, do you consider gene therapies?\*

\* Among those familiar with therapeutic approach

Therapeutic Approach	Total n = 47-230	Non-Academic n = 20-122	Academic n = 27-108
<b>CRISPR</b> clustered short palindromic repeats	92 %	91 %	93 %
<b>TALENS</b> transcription activator-like effector nuclease	72 %	70 %	74 %
<b>AAV</b> adeno-associated virus	67 %	59 %	76 %
<b>RNAi</b> RNA interference	54 %	57 %	52 %
<b>siRNA</b> short interfering RNAs	53 %	59 %	49 %
<b>ASO</b> antisense oligonucleotides	51 %	62 %	43 %
<b>mRNA</b> messenger RNA	48 %	55 %	41 %



# Therapeutic Approach Top Associations

Oncologists and physicians at academic practices are most able to accurately identify CRISPR, TALENS, and AAV as therapies that make changes at the DNA level.

## Q3a

Select the term(s) that best answers each of the statements provided below.

✓ Indicates correct answer

## Statement

Involves intentional and permanent changes at the DNA level

	Total n=250	PCP n=120	Onc n=80	Ped n=50	Non-Acad n=132	Academic n=118
✓ <b>CRISPR</b>	<b>58%</b>	52%	<b>75%</b>	48%	52%	65%
<b>Unsure</b>	<b>21%</b>	21%	15%	32%	28%	14%
<b>mRNA</b>	<b>18%</b>	24%	6%	22%	19%	17%
✓ <b>AAV</b>	<b>16%</b>	13%	25%	10%	11%	22%
✓ <b>TALENS</b>	<b>15%</b>	14%	19%	10%	10%	20%
<b>RNAi</b>	<b>13%</b>	19%	5%	10%	11%	14%
<b>siRNA</b>	<b>10%</b>	15%	5%	8%	10%	11%
<b>ASO</b>	<b>8%</b>	9%	8%	6%	8%	8%



# Therapeutic Approach Top Associations

Oncologists and physicians at academic practices are also most likely to identify DNA-editing therapies as being at risk for unintended permanent changes.

## Q3a

Select the term(s) that best answers each of the statements provided below.

✔ Indicates correct answer

## Statement

May cause unintended permanent changes at the DNA level

	Total n=250	PCP n=120	Onc n=80	Ped n=50	Non-Acad n=132	Academic n=118
✔ CRISPR	36%	33%	48%	26%	31%	42%
Unsure	35%	31%	29%	54%	43%	25%
✔ TALENS	18%	15%	24%	16%	11%	25%
mRNA	17%	21%	14%	12%	17%	16%
✔ AAV	17%	13%	24%	14%	14%	20%
siRNA	15%	16%	16%	10%	15%	14%
RNAi	13%	14%	14%	10%	11%	15%
ASO	10%	8%	11%	12%	11%	9%





# Therapeutic Approach Top Associations

While oncologists are most able to identify AAV as having potential to make vaccines (39%), pediatricians are most able to discern this about mRNA (34%).

## Q3a

Select the term(s) that best answers each of the statements provided below.

✔ Indicates correct answer

## Statement

Can be used to make vaccines

	Total n=250	PCP n=120	Onc n=80	Ped n=50	Non-Acad n=132	Academic n=118
<b>Unsure</b>	<b>32%</b>	31%	30%	38%	40%	23%
✔ <b>AAV</b>	<b>30%</b>	25%	39%	30%	29%	32%
✔ <b>mRNA</b>	<b>30%</b>	31%	26%	34%	28%	32%
<b>CRISPR</b>	<b>17%</b>	20%	14%	16%	13%	22%
<b>RNAi</b>	<b>17%</b>	24%	11%	10%	14%	20%
<b>siRNA</b>	<b>15%</b>	17%	14%	12%	10%	20%
<b>ASO</b>	<b>10%</b>	8%	14%	6%	9%	10%
<b>TALENS</b>	<b>7%</b>	9%	6%	4%	8%	6%



# Therapeutic Approach Top Associations

All physicians segments have poor awareness of approved nucleic-acid therapies. Physicians incorrectly chose not approved therapies (unsure below), CRISPR, or mRNA as the top three answers.

## Q3a

Select the term(s) that best answers each of the statements provided below.

## Statement

Has already yielded FDA-approved medicines

	Total n=250	PCP n=120	Onc n=80	Ped n=50	Non-Acad n=132	Academic n=118
<b>Unsure</b>	<b>59%</b>	51%	64%	72%	61%	57%
<b>CRISPR</b>	<b>18%</b>	25%	11%	14%	17%	20%
<b>mRNA</b>	<b>11%</b>	16%	6%	8%	10%	13%
✓ <b>AAV</b>	<b>10%</b>	4%	15%	14%	8%	11%
✓ <b>siRNA</b>	<b>8%</b>	12%	8%	2%	6%	11%
✓ <b>RNAi</b>	<b>8%</b>	13%	5%	2%	8%	8%
✓ <b>ASO</b>	<b>6%</b>	5%	6%	8%	6%	6%
<b>TALENS</b>	<b>3%</b>	3%	3%	2%	4%	2%

✓ Indicates correct answer



# Most Promising Therapy BY SPECIALTY

While all 27% of all physicians find CRISPR the most promising therapeutic approach, 16% of PCPs find that mRNA therapy has the most potential.

## Q4

Please identify which one of the following approaches you believe holds the most promise for improving the lives of your patients. Please explain your choice.

Therapeutic Approach	Total n=250	PCP n=120	Onc n=80	Ped n=50
<b>CRISPR</b> clustered short palindromic repeats	27%	20%	44%	22%
<b>mRNA</b> messenger RNA	8%	16%	4%	2%
<b>AAV</b> adeno-associated virus	3%	6%	0%	2%
<b>RNAi</b> RNA interference	3%	2%	6%	2%
<b>ASO</b> antisense oligonucleotides	2%	3%	3%	0%
<b>siRNA</b> short interfering RNAs	2%	2%	4%	0%
<b>TALENS</b> transcription activator-like effector nuclease	1%	2%	0%	0%
<b>Unsure</b>	50%	50%	40%	58%



























# Most Promising Therapy BY PRACTICE SETTING

Those in academic vs. non-academic practices yield similar proportions of choices for most promising therapies.

## Q4

Please identify which one of the following approaches you believe holds the most promise for improving the lives of your patients. Please explain your choice.

Therapeutic Approach	Total n=250	Non-Academic n=132	Academic n=118
<b>CRISPR</b> clustered short palindromic repeats	 27 %	 27 %	 30 %
<b>mRNA</b> messenger RNA	 8%	 11 %	 7%
<b>AAV</b> adeno-associated virus	 3%	 2%	 4%
<b>RNAi</b> RNA interference	 3%	 2%	 4%
<b>ASO</b> antisense oligonucleotides	 2%	 2%	 3%
<b>siRNA</b> short interfering RNAs	 2%	 2%	 3%
<b>TALENS</b> transcription activator-like effector nuclease	 1%	 1%	 2%
<b>Unsure</b>	 50 %	 52 %	 48 %





# Questions?

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For more information, please contact:

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