

EXPLORING ATTITUDES TOWARDS NEWLY APPROVED THERAPEUTICS IN  
PRENATAL GENETIC COUNSELING PRACTICE

Charlotte Close

May 2021

---

Submitted in partial fulfillment  
of the requirements for the degree of  
Master of Science in Human Genetics  
Sarah Lawrence College

Funding support: The National Society of Genetic Counselors CF and CFTR Spectrum Special  
Interest Group.

## ABSTRACT

Cystic fibrosis (CF) care has rapidly evolved over the past decade due to the introduction of CFTR modulators and continued quality improvement efforts, yet research from 2013 suggests that prenatal genetic counselors often did not feel knowledgeable discussing newer CF treatments with patients and expressed the need to refer to a CF specialist (Elsas, 2017). Given that the intervening years have allowed for collection of long-term data about CFTR modulators and that the recently approved modulator Trikafta (tez/elx/iva) is available to 90% of the CF population, it is appropriate to re-evaluate the status of prenatal genetic counselors' awareness of and attitudes towards discussing newly approved treatments with patients. The present study aimed to gather that information and to analyze how likely counselors were to discuss quality of life and treatment of CF with prospective parents experiencing a prenatal diagnosis of CF. Members of the NSGC Prenatal Special Interest Group (N=866) were provided with information about the status of currently approved CFTR modulators and assessed before and after viewing the information. They were presented with clinical scenarios and asked to rate their perceived impact of CF and CF treatments along with the likelihood that they would discuss potential benefits and limitations with parents experiencing a prenatal diagnosis. Of the 866 members surveyed, 53 (6.12%) completed the questionnaire. Results indicated that nearly all (98.11%) respondents had heard of CFTR modulators and were not concerned about instilling false hope (84.9%) when discussing them with prenatal patients. The majority agreed that providing information about Trikafta (elx/tez/iva) could affect pregnancy management decisions (58.49%). Compared to most respondents (79.25%) who would discuss the availability of gene therapies for genetic conditions such as SMA and sickle cell disease, only about half of respondents would mention Trikafta (tez/elx/iva) to patients directly but would refer patients to a CF specialist. These data suggest that even when prenatal genetic

counselors are familiar with new CF treatment options, they are influenced by their perceived impact of those treatments and their understanding of a genetic counselor's role. Further clinical guidance regarding discussion of newly approved CF treatments as well as the development of clear definitions of specialty roles within the genetic counseling field are needed.

Key words: Cystic fibrosis, prenatal diagnosis, prenatal genetic counseling, Trikafta (tez/elx/iva), targeted treatments

## **ACKNOWLEDGMENTS**

I would like to extend my sincere thanks to: Elinor Langfelder-Schwind, MS, CGC for her guidance at every stage of this research project, Susanna A. McColley, MD for her insightful comments and suggestions, Chantal Duteau Buck, MS, CGC for her unwavering support and advice, and The National Society of Genetic Counselors CF and CFTR Spectrum Special Interest Group for their financial contribution without which this project would not have been possible.

## Table of Contents

<b>Background .....</b>	<b>1</b>
Cystic fibrosis (CF) .....	1
CFTR Modulator Therapies .....	2
Early Diagnosis of CF .....	5
Prenatal Diagnosis of CF .....	5
Genetic Counseling of CF .....	6
<b>Methods .....</b>	<b>8</b>
Study design.....	8
Selection of Participants and Data Collection .....	9
Ethical considerations.....	10
Data analysis .....	10
<b>Results.....</b>	<b>11</b>
Professional experience.....	11
Perceptions of prenatal GC scope of practice .....	13
Knowledge of and experience with targeted treatments .....	15
Perceptions of Trikafta (elx/tez/iva).....	17
Perception of General Treatment Discussions .....	22
<b>Discussion .....</b>	<b>22</b>
Limitations .....	26
Future directions .....	27
Limitations & future directions .....	28
<b>Conclusion .....</b>	<b>29</b>
<b>Figures .....</b>	<b>29</b>
<b>Bibliography .....</b>	<b>30</b>
<b>Appendices.....</b>	<b>37</b>
Appendix A: Survey.....	37
Appendix B: Recruitment Message .....	39
Appendix C: Consent Form .....	41
Appendix D: CFTR Modulator Information.....	52

## **BACKGROUND**

### **Cystic Fibrosis**

Cystic fibrosis (CF) is a multisystem recessive genetic condition characterized by progressive lung disease, chronic lung infections, and pancreatic insufficiency. CF was first described in 1938 as a uniformly fatal disease of the infant, and now national registry data predicts that of babies born with CF in 2018, half are projected to live to 47 years or older (Anderson, 1932; Cystic Fibrosis Foundation Patient Registry, 2019). Life expectancy has steadily increased over time as understanding of the underlying mechanisms of disease informed new treatment modalities and quality improvement efforts (Bell, 2019). These mechanisms were identified through the cloning of the cystic fibrosis transmembrane regulator gene (CFTR) and the annotation of more than 2000 variants within the gene, of which upwards of 1700 are known to cause CF (Dorfman, 2011; CFTR2@JohnsHopkins). Pathogenic CFTR variants disrupt the function of the CFTR protein, an epithelial anion channel that transports Cl<sup>-</sup> and HCO<sub>3</sub><sup>-</sup> across membranes in organs including the gastrointestinal and respiratory tracts (Middleton, 2019). Functioning CFTR protein is necessary to maintain the fluid balance within mucus and consequently, malfunctioning CFTR leads to collection of thick mucus in various organs causing obstruction and infection (Bell, 2020).

The most common CFTR pathogenic variant is F508del (also known as p. Phe508del) with 90% of all individuals with CF carrying at least one copy of F508del (Cystic Fibrosis Foundation Patient Registry, 2020). At a molecular level, F508del disrupts CFTR protein function by causing defective intracellular processing which results in misfolded proteins that are degraded before they can make it to the cell surface (Middleton, 2019). Most other CFTR variants are rare and exist in <5% of individuals and families with CF. The rarity of these variants creates challenges in diagnosis and treatment (Bell, 2020).

Of note, there is significant variability in genotype frequency among CF patients, including F508del. Genotype is closely linked to ancestry and ethnicity, with F508del being the predominant pathogenic variant among CF patients who identify as white. Conversely, the likelihood of nonwhite CF patients carrying a non-F508del variant is 17%, 30%, 38%, and 40% of those with Native American, Hispanic, Black, and Asian backgrounds respectively (Schrijver, 2016). The spectrum of CFTR variants among non-white individuals has not been fully defined and this has implications for diagnostic testing, targeted treatment eligibility and ultimately morbidity and mortality among those populations (McGarry, 2019).

### **CFTR Modulator Therapies**

CF treatment has evolved in the past decade from being primarily focused on symptom - based treatment towards molecular - based therapies that target and correct the specific underlying defects in the CFTR protein (Foil, 2019). This new class of CFTR modulator drugs approved to treat CF are divided into two subclasses: 1) potentiators which increase the amount of time the CFTR ion channel is open and 2) correctors which rectify the folding of the CFTR protein and improve localization to the cellular membrane (Clancy, 2018).

In 2012 the first CFTR modulator, ivacaftor (Kalydeco), was approved in the US. Ivacaftor is a potentiator of the protein carrying the G551D variant and was shown to improve lung function, increase weight and significantly reduce the number of pulmonary exacerbations in those treated compared to those on placebo. Following this breakthrough, three more CFTR modulators have been approved in the US, as of 2020, which include various combinations of potentiators and correctors that target specific genotypes (Table 1). The term “next generation” refers to elexacaftor having a different, yet efficacious, mechanism of action than first generation correctors including tezacaftor (Ridley, 2020).

Brand Name	<b>Kalydeco</b>	<b>Orkambi</b>	<b>Symdeko</b>	<b>Trikafta</b>
Medication	Ivacaftor	Lumacaftor/ Ivacaftor	Tezacaftor/ Ivacaftor	Elexacaftor/ Tezacaftor/ Ivacaftor
Drug Class	Potentiator	Corrector and potentiator	Corrector and potentiator	Corrector, potentiator, and next generation corrector
FDA Approval Date	Jan 31, 2012	Jul 2, 2015	Feb 12, 2018	Oct 21, 2019

Table 1: FDA approved CFTR modulators as of December 2020

As of December 2020, Trikafta (elx/tez/iva) was available to any individual heterozygous for one copy of F508del and was age 12 years or older (Vertex, 2020). This translates to approximately 90% of the CF population in the US (roughly 27,000 individuals in total) being eligible for this modulator therapy (Cystic Fibrosis Foundation Patient Registry, 2019). Two trials proved the efficacy of Trikafta (elx/tez/iva). The first (VX17-445-102) was a randomized, double-blind, placebo-controlled trial enrolling 403 patients who were 12 years of age or older with cystic fibrosis with Phe508del–minimal function genotypes (Middleton, 2019). Minimal function genotypes are classified as such due to their insufficient protein production (ex. nonsense mutation G542X) as well as insufficient in vitro response to ivacaftor and tezacaftor-ivacaftor (ex. CFTR missense mutation N1303K) (Taylor-Cousar, 2019). The second (VX17-445-103) was a randomized, double-blind, active-controlled trial enrolling 113 participants with cystic fibrosis homozygous for the F508del mutation, aged 12 years or older (Heijerman, 2019). Both of these trials demonstrated that Trikafta (elx/tez/iva) contributed to improvements in markers of CF disease progression. These primary outcomes (Table 2) included: significant improvements of pulmonary function tests, significant reduction of pulmonary exacerbations, higher patient

reported quality of life, and normalization of sweat chloride levels compared to controls (Heijerman, 2019; Middleton, 2019).

<b>Study Participant Genotypes</b>	<b>Control</b>	<b>ppFEV<sub>1</sub></b>	<b>Pulmonary Exacerbation Rate</b>	<b>Respiratory Domain Score on the CFQ-R</b>	<b>Sweat Chloride Levels</b>
F508del/ F508del	Tezacaftor / Ivacaftor	10.0 points higher	10% lower	17.4 points higher	45.1 mmol per liter lower
F508del/ Minimal Function	Placebo	14.3 points higher	63% lower	20.2 points higher	41.8 mmol per liter lower

Table 2: Endpoint measurements as compared to the control group at the end of the trial period.

ppFEV<sub>1</sub>= percent predicted forced expiratory volume in one second. CFQ-R = Cystic Fibrosis Questionnaire-Revised. (Heijerman, 2019; Middleton, 2019).

This shift from the management of downstream manifestation of basic CFTR defects towards focusing on the protein damage itself is revolutionizing CF care. Knowledge of a patient’s genotype was once most helpful for diagnosis and research but is now an essential component of treatment decision making (Foil, 2019). The concept of ‘theratyping’ has recently arisen as a method of grouping CFTR variants according to their effect on the CFTR protein and in response to corrector and potentiator compounds (Cutting, 2015). Data gathered from theratyping efforts could more thoroughly characterize rare or complex CFTR variants and enable individuals who are not typically included in clinical trials access to CFTR modulators (Clancy, 2019). With the advent of targeted therapeutics within CF care, more focused and patient specific counseling and decision making is to be expected.

## **Early Diagnosis of CF**

The earlier a diagnosis of CF is established, the better the prognosis, therefore, diagnostic recommendations are an important component to the continued improvement of predicted survival rates. Currently, recommended screening methodologies including: evaluation of parental carrier status, prenatal ultrasound checking for CF associated markers, and newborn screening (NBS), have advanced the timeline of CF diagnosis ahead of the historical recognition of characteristic clinical signs and symptoms (Foil, 2019). It is recommended that the diagnosis of CF be determined through an evaluation of CFTR function with a measurement of sweat chloride levels (Farrell, 2017).

## **Prenatal Diagnosis of CF**

Prenatal diagnosis of CF involves testing a pregnancy via chorionic villus sampling (CVS), and/or amniocentesis, for pathogenic variants (Castellani, 2010). Importantly, the face of prenatal diagnosis may be changing with new technologies on the horizon that include reliable non-invasive prenatal testing that utilizes an ultra-sensitive targeted next generation sequencing method for haplotype-based paternal allele exclusion testing of CFTR within 8 weeks of gestation (Zeevi, 2018)

A presumptive prenatal diagnosis is defined as molecular testing showing 2 CF-causing CFTR mutations (in trans, as confirmed by parental testing). Once this presumptive diagnosis is made and pregnancy is carried to term, it is recommended that newborns greater than 36 weeks gestation and >2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 d of age, ideally by the end of the neonatal period (4 weeks of age). This turnaround time reflects the importance of

early diagnosis because clinical signs including malnutrition may present by as early as two weeks (Farrell, 2017).

### **Genetic Counseling of CF**

As mentioned earlier, there is a new tendency to call variants on their potential response to modulator therapies rather than on their functional class. Genetic counselors are having to advise patients and families with both the function and therapeutic response of variants in mind. Counselors are also often being asked to predict genotype-phenotype correlations with the awareness that discussion of variants associated with mild disease could affect carrier parents' decisions about whether to terminate a current pregnancy and/or pursue PGD in the future (Foil, 2019).

The role of a genetic counselor is to provide information about genetic conditions, including education about management, prevention, resources and research, and counseling to promote informed choices and adaptation to the risk or condition (National Society of Genetic Counselors' Definition Task Force, 2006). Therefore, genetic counselors have had to grow with the increased research on and understanding of CF, a condition which was once used as a textbook example of a simple Mendelian condition. In 2017, a study of genetic counselors working in prenatal settings found GCs often did not feel knowledgeable discussing newer CF treatments and expressed the need to refer to a CF specialist to initiate these discussions (Elsas, 2017).

In the context of a prenatal diagnosis of CF, genetic counselors are a source of education and represent an important variable that can influence informed decision making and consequently influence clinical outcomes including termination of pregnancy. Recent studies have found that almost all high-risk pregnancies that test positive for CF are terminated. In other words, prenatal testing leads to management changes that result in fewer CF-affected births (Kessles, 2020). There

is an ongoing need for exploration of whether sufficient education and counseling is provided to high-risk couples faced with a prenatal diagnosis of CF. Additionally, as patient advocates, genetic counselors have an obligation to understand the clinical relevance of new treatments and the benefits, costs, and limitations of said treatments so that they can decide when it would be beneficial to share information about treatments with patients.

Elsas et al. (2017) explored the attitudes of prenatal genetic counselors toward discussion of novel approved and experimental CF treatments in the prenatal setting. In the context of the 2012 FDA approval of Kalydeco (iva) it was found that a counselor's familiarity with a new treatment option, their impression of its benefits and limitations, their comfort discussing general treatment options, and their understanding of the genetic counselor's role are predictive of their perspective on sharing information about a new treatment (Elsas, 2017). Elsas et al. (2017) pointed out that education of genetic counselors on new treatment options and a clearer identification of the role of a genetic counselor in a prenatal setting were needed.

In the years since 2013, when the Elsas survey was given, three additional CFTR modulators have been approved by the FDA. Awareness of modulator availability by genetic counselors has ostensibly risen and requires updating. It is appropriate to reevaluate the status of genetic counselors' attitudes towards and awareness of newly approved therapeutics for CF and to utilize that data to analyze how likely counselors would be to discuss quality of life and treatment of CF with prospective parents. Particularly, this evaluation should take place with respect to the most recently approved modulator, Trikafta (elx/tez/iva) because of its expanded eligibility and efficacy data.

## **METHODS**

An online survey was developed to explore what prenatal genetic counselors currently know about FDA approved targeted therapeutics for CF, and how subsequent education about those therapeutics might impact their counseling of a prenatal diagnosis of CF. The participants make up a cohort of prenatal genetic counselors and their selection is based on membership of the National Society of Genetic Counselors (NSGC) Prenatal Special Interest Group (SIG).

### **Study design**

This study was conducted on SurveyMonkey's online platform. It took approximately 8 - 10 minutes to complete and consisted of an educational overview of CF, an educational intervention describing the current status of CFTR modulator therapies, and 22 total questions (see Appendix A). These questions were composed of multiple choice, open-ended and Likert scale questions. This study was modeled on the structure of work by Elsas, 2016.

First, electronic consent was obtained, and an educational overview of CF was provided for participants to read (see Appendix C). This was followed by a series of demographic questions. Subsequently, a theoretical clinical scenario of a prenatal diagnosis of CF was presented. Participants were asked to rate their perception of the impact that a CF diagnosis has on life expectancy, physical health, psychological and emotional health, social functioning and personal goal fulfillment, and child's daily care. These five categories were adapted from a validated quality of life questionnaire called the Cystic Fibrosis Questionnaire-Revised (CFQ-R). The CFQ-R is most often used in clinical research and therefore describes the patient's time and energy devoted to health maintenance as "treatment burden". The phrasing of this category was changed for the purposes of this study to "child's daily care" to make the language more accessible to genetic

counselors. Following this first question, participants reported the likelihood that they would discuss with patients the impact that CF would have on each of the five categories.

Knowledge of CFTR modulators and general CF therapies was then assessed. An educational intervention followed these questions summarizing the status of Kalydeco (iva), Orkambi (lum/iva), Symdeco (tez/iva) and Trikafta (elx/tez/iva) as of November 2020 (see Appendix D).

A second mock scenario was presented with the stipulation that the pregnancy had a genotype eligible for Trikafta (elx/tez/iva). The participants were then asked to rate the likelihood that they would discuss the impact that Trikafta (elx/tez/iva) would have on the five categories with the theoretical patients as well as rate their likelihood of sharing additional information concerning Trikafta (elx/tez/iva). Lastly, participants were asked to rate their level of agreement with several statements exploring counselor's reasoning for discussing Trikafta (elx/tez/iva) and other newly approved therapies in the prenatal setting. A copy of the full survey can be found in Appendix A

### **Selection of Participants and Data Collection**

The study was open from December 21, 2020 through February 11, 2021. Only individuals who are American Board of Genetic Counseling (ABGC) board-certified or board-eligible genetic counselors and currently provide prenatal or preconception genetic counseling services to patients in the United States are eligible to participate. In an attempt to increase response rate by sampling only members of the target population, prenatal genetic counselors, the survey was distributed through an ad-hoc eblast to the NSGC Prenatal SIG rather than to the entire NSGC membership.

During the time the survey was open, three emails were sent to the NSGC Prenatal SIG requesting that members take part in the study. These emails included the message found in

Appendix B and intentionally avoided mention of Trikafta (elx/tez/iva) so that participants could be surveyed about their prior knowledge of Trikafta (elx/tez/iva) without sampling bias.

The Prenatal SIG had 866 members as of December 21, 2020, and 67 of those members responded to the survey. Of those 67 participants, 53 participants completed the full survey and were deemed eligible for inclusion in data analysis. Only complete responses were accepted due to the study's data analysis, which draws correlations between each respondent's demographic information, background knowledge of the topics at hand, perceived impact of CFTR modulator treatments, and likelihood to discuss specific topics with patients. This filtering resulted in a final response rate of (6.12%).

### **Ethical considerations**

The consent form can be found in Appendix C and was completed by participants before they began the study. If participants did not consent to voluntarily participate in the study, they were disqualified. This was approved by the Sarah Lawrence College Institutional Review Board on December 3, 2020 when this study was determined to be exempt. This research protocol falls under exemption 2, which states that research involving survey procedures can be exempt from review as long as participants cannot be identified or that disclosure of their identity outside of the research would not put them at risk of harm. No identifying information including IP address, email address, first or last names were gathered through the SurveyMonkey platform.

### **Data analysis**

Data analysis took place within two platforms. SurveyMonkey was used for univariate analysis and chart development. Bivariate analysis and statistical computations were calculated within Microsoft Excel Version 16.46.

## RESULTS

### Professional experience

This study's participants had a variety of backgrounds and experiences. The average number of years that participants had been practicing as prenatal genetic counselors was 7 years with a mean of 7 years. Most of these participants worked at University Hospitals and the full breakdown of work environments can be found in Chart 1.

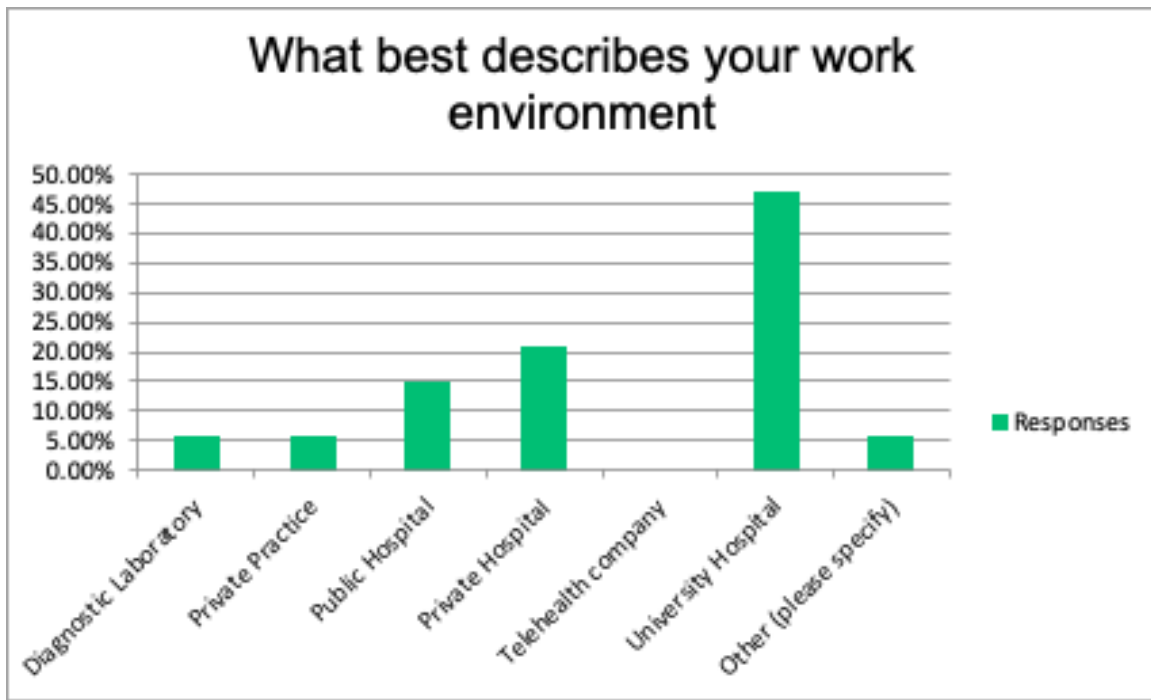


Chart 1: Question 5. Other responses include: Military Hospital, Non-profit genetic counseling organization, and University-affiliated group practice

### Experience with CF

The majority of participants (60.38%) see 0-1 prenatal CF diagnoses a year with 39.62% seeing 2-5 a year. No participants reported seeing more than 5 prenatal CF diagnoses a year. Of the participants, the majority (84.91%) did not have any specialized experience of CF, the full breakdown of experience can be found in Chart 2, and the majority (56.6%) did not work at an institution formally associated with an accredited CF center. Nevertheless, the majority of

participants (79.75%) always refer to or recommend an accredited CF center when a prenatal diagnosis is made, the full breakdown of these responses can be found in Chart 3.



Chart 2: Question 7

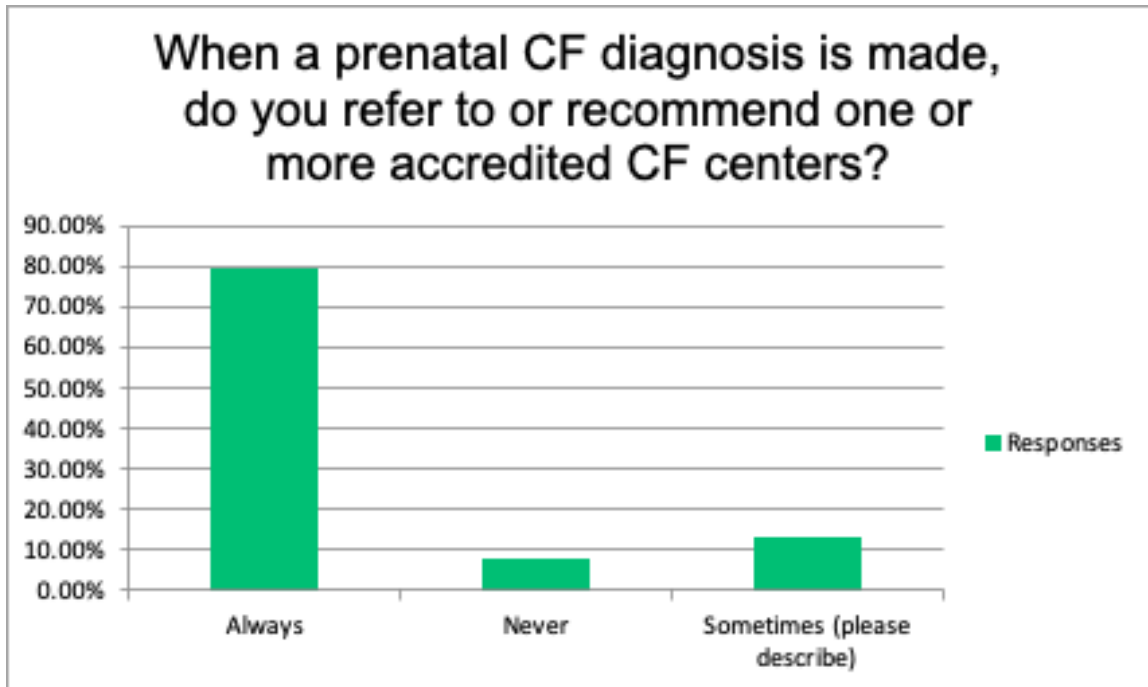


Chart 3: Question 9. Sometimes responses include: 5 individuals for whom this situation has not come up yet, 1 individual who bases referral on the request of the patient, and 1 individual who reported that “Not all families are open to referral to a CF center (i.e., couples who come into pregnancy having already decided on termination for affected pregnancy).”

### **Perceptions of prenatal GC scope of practice**

Participants were presented with a scenario in which a couple is referred after prenatal diagnosis reveals that their pregnancy carries two pathogenic CFTR variants and will be affected by classic cystic fibrosis (CF). They were then asked to estimate the impact that CF would have on measures of quality of life by rating 1 (little or no impact) to 4 (profound impact), these results can be found in Table 3. Next, participants were asked to estimate their likelihood of discussing the impact that CF would have on those same measures of quality of life by rating 1 (definitely not) to 4 (definitely), these results can be found in Table 4.

	Little to no impact (1)	Some impact (2)	Significant impact (3)	Profound impact (4)	Weighted Average (n = 53)	Standard Deviation
Life Expectancy	0%	43.4%	<b>47.17%</b>	9.43%	2.66	.23
Physical Health	0%	11.32%	<b>69.81%</b>	18.87%	3.08	.29
Psychological and Emotional Health	0%	42.31%	<b>51.92%</b>	5.77%	2.63	.25
Social Functioning and Personal Goal Fulfillment	9.62%	<b>75%</b>	13.46%	1.92%	2.08	.31
Child's Daily Care	0%	22.64%	<b>64.15%</b>	13.21%	2.91	.26

Table 3: Estimate the impact that CF will have on the following (Question 10)

	Definitely	Probably	Probably Not	Definitely Not	Weighted Average (n = 53)	Standard Deviation
Life Expectancy	<b>69.81%</b>	28.3%	1.89%	0%	1.32	.30
Physical Health	<b>86.79%</b>	13.21%	0%	0%	1.13	.38
Psychological and Emotional Health	28.3%	<b>50.94%</b>	20.75%	0%	1.92	.21
Social Functioning and Personal Goal Fulfillment	21.15%	<b>61.54%</b>	15.38%	1.92%	1.98	.25
Child's Daily Care	<b>58.49%</b>	32.08%	9.43%	0%	1.51	.26

Table 4: In counseling the couple, would you plan to address the impact of CF on the following: (Question 11)

Correlations between the participants' perceived impact of CF on each measure of quality of life and their likelihood of discussing that impact were calculated. In order from strongest to weakest the correlations were: Child's daily care:  $r(53) = 0.4555$   $p = 0.0003$ , Physical Health:  $r(53) = 0.358$   $p = .004$ , Psychological & Emotional Health:  $r(53) = 0.184$   $p = 0.093$ , Life Expectancy:  $r(53) = 0.129$   $p = 0.178$ , Social Functioning & Personal Goal Fulfillment:  $r(53) = .043$   $p = .381$ .

## **Knowledge and experience with targeted treatments**

Familiarity with CFTR modulator therapies was assessed by asking participants to indicate their level of knowledge of modulators. The majority of participants (71.70%) knew a little bit about them, the full breakdown can be found in Chart 4. Notably, Trikafta (elx/tez/iva) was discussed at the 2020 NSGC Annual Educational Conference by CF patient advocate Gunnar Esiason. Participants were asked if they first heard of Trikafta (elx/tez/iva) during this event and 9.43% of participants reported that this was in fact their first-time hearing of it.

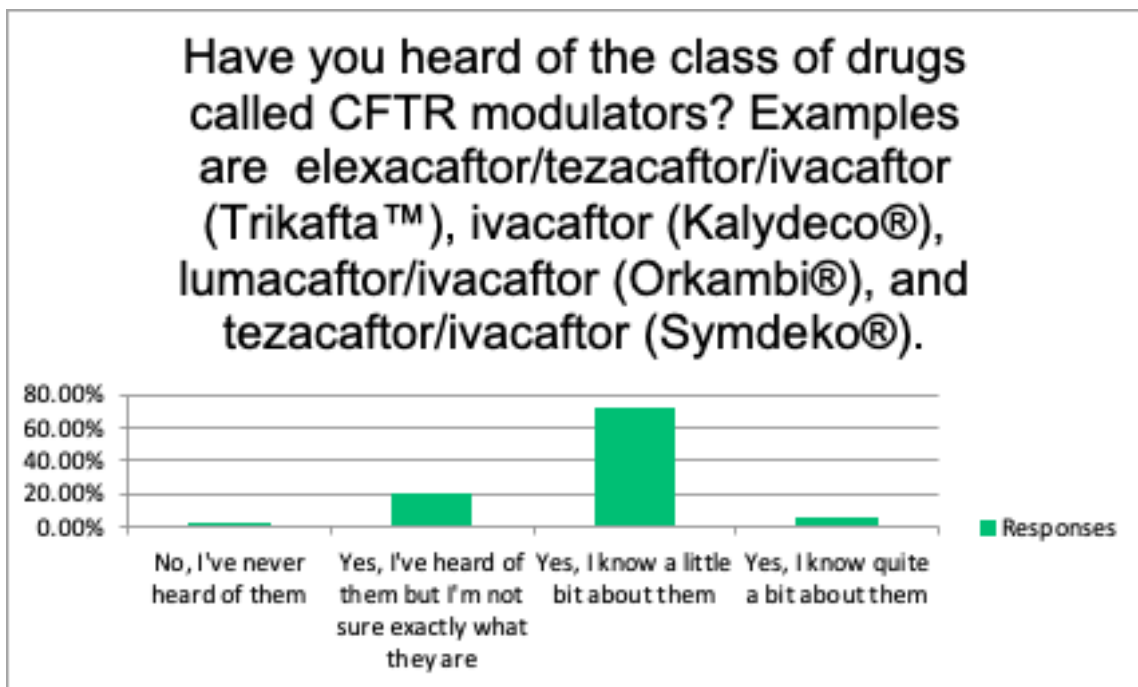


Chart 4: Question 12

The perceived importance of prenatal genetic counselors' having knowledge of treatment options for CF was assessed by asking participants to rate importance from extremely important to not at all important or only important for those counseling at a CF center or only important for those counseling a family after the birth of an affected child; these results can be found in Chart 6. It was identified that 80% of prenatal genetics generally discuss improving treatment options for CF with patients while 16.98% do not.

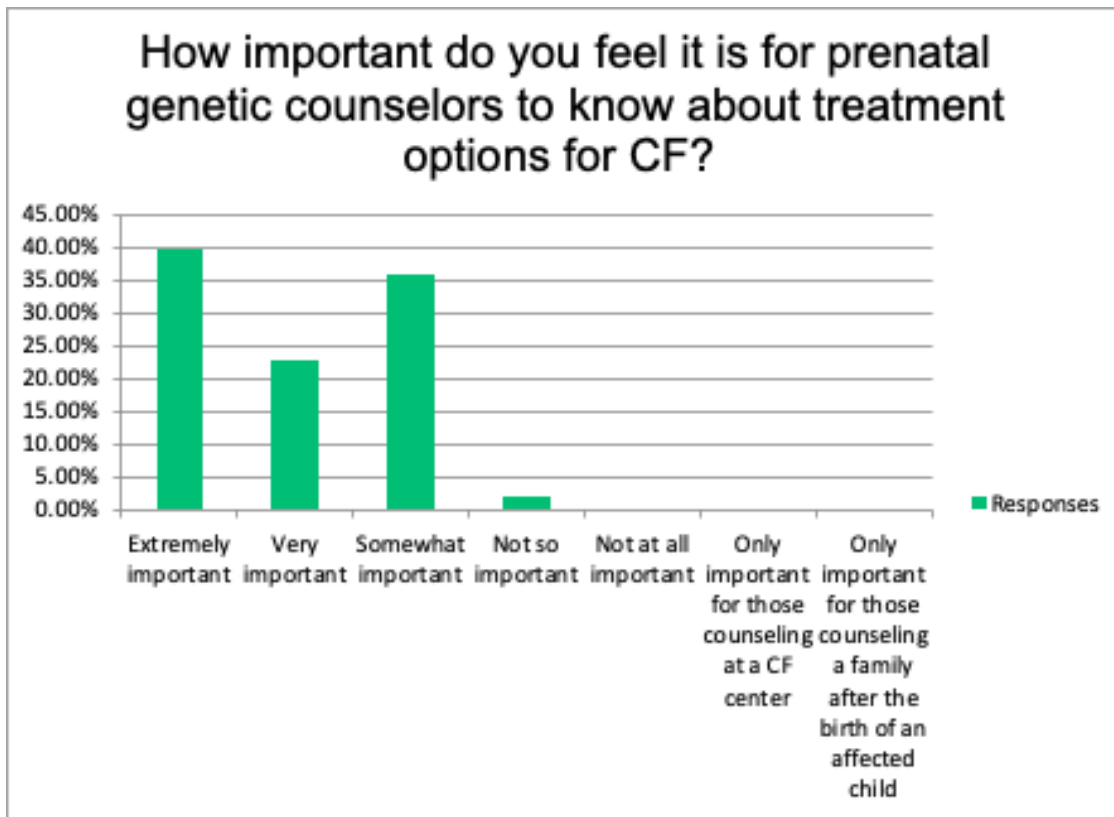


Chart 6: Question 15

The resources from which prenatal genetic counselors typically learn about new treatments were examined and the top resources identified were Lectures and Conferences (100%), Colleagues (77.36%), Professional Practice Guidelines (54.72%), and Scientific Journal Articles (54.72%); the full breakdown of responses can be found in Table 5.

Answer Choices	Responses	
Colleagues	<b>77.36%</b>	41
CF Team or CF Team Specialists	32.08%	17
Drug Manufacturers	5.66%	3
FDA	1.89%	1
Lectures and Conferences	<b>100.00%</b>	53
Media	32.08%	17
Patient Advocacy Organizations	22.64%	12
Patients	20.75%	11
Professional Practice Guidelines	<b>54.72%</b>	29
Scientific Journal Articles	<b>54.72%</b>	29
Other (please specify)	5.66%	3

Table 5: From which of the following resources do you typically learn about new treatment options for CF? (choose all that apply): (Question 16)

### **Perceptions of Trikafta (elx/tez/iva)**

Participants were presented with an educational intervention (a copy of this intervention can be found in Appendix D) describing FDA approved CFTR modulators, as of November 2020. After reading this information, participants were asked about a second clinical scenario. This scenario involves a couple who were referred after prenatal diagnosis reveals that their pregnancy carries two pathogenic CFTR variants and will be affected by classic cystic fibrosis (CF). The genotype includes at least one copy of F508del. Participants were asked if they would plan to address the effect that Trikafta (elx/tez/iva) would have on measures of quality of life by rating 1 (little or no impact) to 4 (profound impact), these results can be found in Table 6.

	Little to no impact (1)	Some impact (2)	Significant impact (3)	Profound impact (4)	Weighted Average (n = 53)	Standard Deviation
Life Expectancy	4.08%	40.82%	<b>44.9%</b>	10.2%	2.61	.21
Physical Health	2%	30%	<b>54%</b>	14%	2.8	.22
Psychological and Emotional Health	6.12%	<b>57.14%</b>	30.61%	6.12%	2.37	.24
Social Functioning and Personal Goal Fulfillment	6%	<b>54%</b>	34%	6%	2.4	.23
Child's Daily Care	6%	<b>46%</b>	44%	4%	2.46	.23

Table 6: Would you plan to address the impact of Trikafta (ELX/TEZ/IVA) on the following: (Question 18)

Correlations between the participants' perceived impact of CF on each measure of quality of life and their likelihood of discussing the impact that Trikafta (elx/tez/iva) on those measures were calculated. In order from strongest to weakest the correlations were: Physical Health:  $r(53) = 0.347$   $p = 0.005$ , Child's Daily Care:  $r(53) = 0.299$   $p = 0.015$ , Life Expectancy:  $r(53) = 0.194$   $p = 0.082$ , Psychological and Emotional Health:  $r(53) = 0.179$   $p = 0.100$ , Social Functioning & Personal Goal Fulfillment:  $r(53) = 0.158$   $p = 0.129$ .

Participants were asked to rank their level of likelihood to share certain aspects of information about Trikafta (elx/tez/iva) and these results are shown in Table 7. Overall, the counselors were in relative consensus that they would refer to a specialist while they varied on how much additional information they would share.

	Extremely likely	Somewhat likely	Neither likely nor unlikely	Somewhat unlikely	Extremely unlikely	Weighted Average
The name of the drug	20.75%	<b>30.19%</b>	15.09%	26.42%	7.55%	2.7
The molecular basis of the drug	7.55%	<b>24.53%</b>	<b>24.53%</b>	<b>24.53%</b>	18.87%	3.23
Expected benefits of treatment	41.18%	<b>45.10%</b>	9.80%	3.92%	0.00%	1.76
Side effects of treatment	11.32%	28.30%	16.98%	<b>30.19%</b>	13.21%	3.06
Cost of the drug/insurance coverage	15.09%	<b>39.62%</b>	13.21%	24.53%	7.55%	2.7
Current availability of the drug to those 12 years and older	28.30%	<b>35.85%</b>	16.98%	15.09%	3.77%	2.3
Referral to a specialist	<b>84.91%</b>	13.21%	1.89%	0.00%	0.00%	1.17

Table 7: Regarding Trikafta (ELX/TEZ/IVA) , how likely are you to share the following with the patients? (Question 19)

Next, participants ranked their level of agreement with several statements about Trikafta (elx/tez/iva), the results of which can be found in Table 8. Largely, counselors disagreed that they would be instilling false hope by discussing Trikafta (elx/tez/iva) and agreed that they were comfortable discussing Trikafta (elx/tez/iva) despite the lack of long-term data. However, counselors were generally not confident discussing Trikafta (elx/tez/iva) with prenatal patients despite their agreement that information about Trikafta (elx/tez/iva) would affect pregnancy management decisions. Counselors agreed that they knew where to find information about Trikafta (elx/tez/iva) and other new treatment options. They also agreed that it is important for professional organizations to provide guidelines on how and when to discuss Trikafta (elx/tez/iva) in practice.

	Strongly Disagree	Disagree	Neither Disagree nor Agree	Agree	Strongly Agree
Information about Trikafta (ELX/TEZ/IVA) would affect pregnancy management decisions.	1.89%	9.43%	30.19%	<b>45.28%</b>	13.21%
The benefits of Trikafta (ELX/TEZ/IVA) justify any costs and risks of this treatment.	0.00%	15.09%	<b>47.17%</b>	28.30%	9.43%
I am uncomfortable discussing Trikafta (ELX/TEZ/IVA) given the lack of long term data.	9.43%	<b>52.83%</b>	35.85%	1.89%	0.00%
I am comfortable discussing Kalydeco (IVA) and Orkambi (LUM/IVA) with prenatal patients because they have long term data.	1.89%	20.75%	<b>49.06%</b>	24.53%	3.77%
I would discuss treatment availability if the treatment is available by age 2 at the time the infant is expected.	3.85%	11.54%	34.62%	<b>44.23%</b>	5.77%
I would discuss treatment availability if the treatment is available to those age 6 and older at the time the infant is expected.	3.77%	13.21%	<b>41.51%</b>	33.96%	7.55%
I would discuss treatment availability if the treatment is available to those age 12 and older at the time the infant is expected.	3.85%	13.46%	<b>42.31%</b>	34.62%	5.77%
By discussing Trikafta (ELX/TEZ/IVA) with prenatal patients I would be instilling false hope.	11.32%	<b>73.58%</b>	13.21%	1.89%	0.00%
I know where to find information about Trikafta (ELX/TEZ/IVA) and other new treatment options.	0.00%	18.87%	18.87%	<b>56.60%</b>	5.66%
I feel confident discussing Trikafta (ELX/TEZ/IVA) with prenatal patients.	5.66%	<b>43.40%</b>	28.30%	20.75%	1.89%
It is important for professional organizations to provide guidelines on how and when to discuss Trikafta (ELX/TEZ/IVA) in practice.	0.00%	13.21%	30.19%	<b>41.51%</b>	15.09%

Table 8: To what extent do you agree or disagree with the following statements: (Question 20)

Who prenatal genetic counselors felt was the most appropriate to discuss Trikafta (elx/tez/iva) with patients and was assessed and the majority (83.02%) felt that it would be the pediatric pulmonologist or other CF expert; the results can be found in Chart 8.

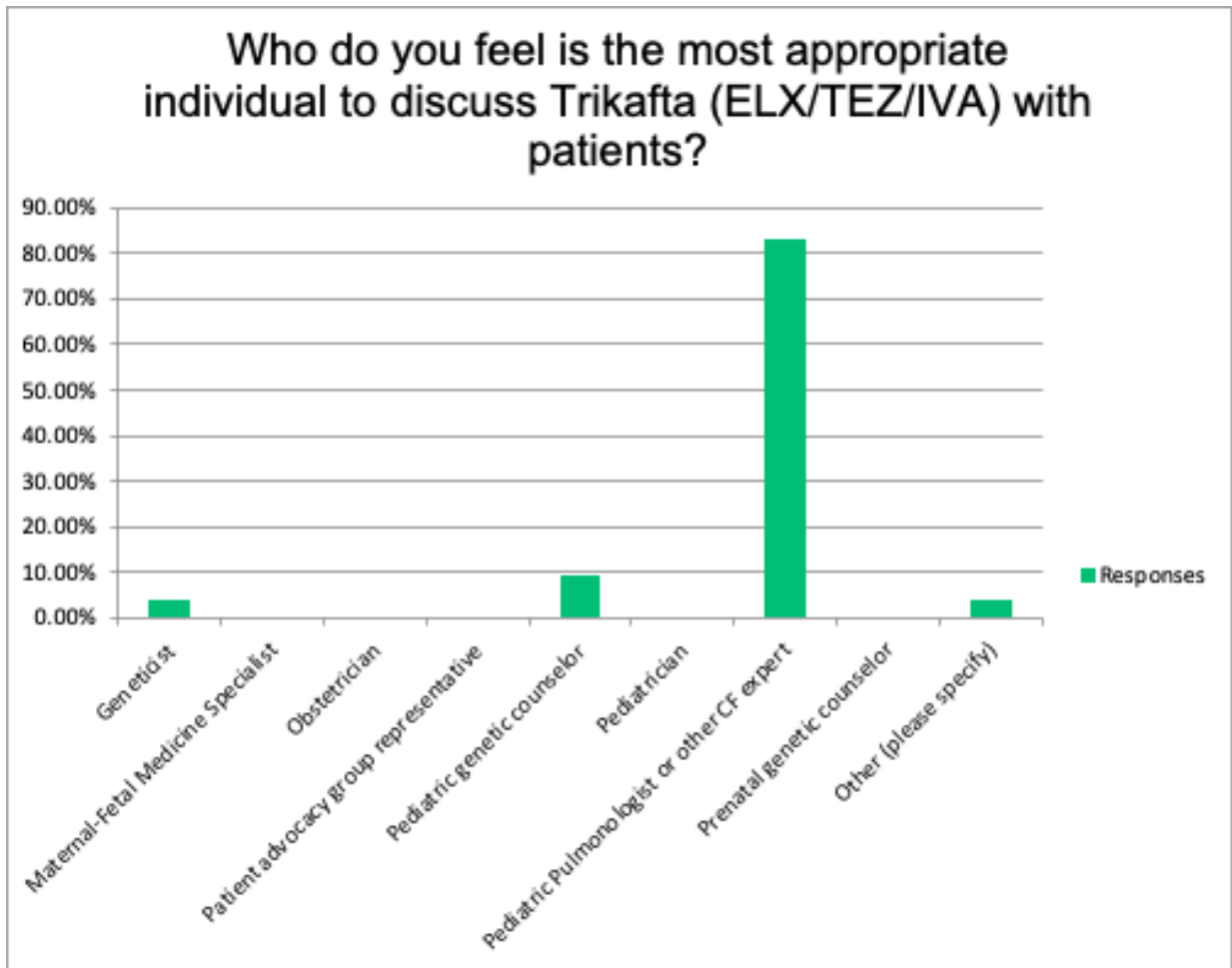


Chart 8: Who do you feel is the most appropriate individual to discuss Trikafta (ELX/TEZ/IVA) with patients? (Question 20) Other responses include: “healthcare providers who come in contact with families faced with CF dx are appropriate to at least discuss trikafta. the CF expert/pulmonologist is most appropriate to discuss details of benefits/limits of treatment” and “depends on the when the diagnosis is made”

## **Perception of General Treatment Discussions**

Lastly participants were asked if they would share information about treatment modalities for other genetic conditions, disorders limiting physical abilities, metabolic conditions, neural tube defects, and conditions with developmental delays or disabilities with prenatal patients. The majority of counselors would share the information of interest. Counselors were most likely to share information about early intervention programs for children with developmental delays or disabilities and least likely to share information about current studies involving investigational therapies that are enrolling individuals with a particular genetic condition; full results can be found in Table 9.

Topic of Interest	Responses
Discussion of successful cases of gene therapies used for genetic conditions such as SMA and sickle cell disease	79.25%
Current studies involving investigational therapies that are enrolling individuals with a particular genetic condition	62.26%
Treatment modalities such as physical and/or occupational therapy for disorders limiting physical abilities	83.02%
Dietary management for metabolic conditions	88.68%
Fetal surgery options in the case of neural tube defects	92.45%
Early intervention programs for children with developmental delays or disabilities	96.23%

Table 9: Would you typically share the following information with prenatal patients when applicable? (Question 22)

## **DISCUSSION**

Since the first genetic counseling training program was founded at Sarah Lawrence College in 1969, the profession has vastly grown and diversified (Stern, 2009). As of 2006, the role of a genetic counselor has been said to include: interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources, and research; and counseling to promote informed choices and adaptation to the risk or condition (Resta, 2006). In 2020, leaders within the genetic counseling field were surveyed to assess the appropriateness of the title “genetic counselor” and the data suggests that though misconceptions of the role of genetic counselors exist, the title itself unifies the field while importantly setting genetic counselors apart from other healthcare professionals (Means, 2020). Many study participants pointed out that genetic counselors’ counseling skill set may become the defining characteristic of the field as the educational role of genetic counselors becomes increasingly dominated by chatbots, algorithms, or web-based videos, etc. (Means, 2020).

In a prenatal setting, genetic counselors are often involved in time-sensitive decision making intertwined with varying degrees of education about the genetic screening, testing, or diagnosis (Beeson, 1979). This process is known to provoke patient anxiety, but the reasoning behind that anxiety has not been fully elucidated. Some research has indicated knowledge of various tests or diagnoses are independent of a patient's attitudes towards those same tests and diagnosis, thus suggesting that interventions aimed at improving informed choice by facilitating patients’ actions to fall in line with their attitudes may be more beneficial than attempting to improve their knowledge (Michie, 2003). Nevertheless, accurate information regarding disease trajectory and medical management has the potential to impact prospective parents' choice to terminate or continue a pregnancy after receiving a prenatal diagnosis (Elsas, 2017).

The results of this project demonstrate variability in the attitudes of prenatal genetic counselors towards newly approved therapeutics for cystic fibrosis as well as an evolution in perspective and knowledge from the results gathered by Elsas et al. (2017). Wide variability in the study population's places of work, number of years practicing, and level of experience with CF were indicated in the survey responses. However, due to the low number of responses to this study, the Elsas et al. (2017) subgroup analysis was not replicated. Nevertheless, the status of genetic counseling practice must be continuously appraised so that the evolving role of genetic counselors can be fully understood. Investigation of this status with respect to cystic fibrosis is imperative because a genetic counselor choosing to or choosing not to mention an FDA-approved treatment could have an impact on pregnancy management decisions.

This study is non-comparative in nature and utilizes an educational intervention about the current status of CFTR modulator treatments for individuals with CF. Data gathered from this study is solely representative of the point in time in which participants were surveyed: between December 2020 and February 2021. This snapshot accounts for growth both patients' and practitioners experience with modulators since the Elsas et al. (2017) study that explored this same question in the context of the 2012 approval of Kalydeco (iva), and the increased availability of modulators due approval of Trikafta (elx/tez/iva). It is postulated that the observation of the longitudinal effects of CFTR modulators has increased genetic counselors' confidence in the impact of modulators on physical health. This confidence has consequently increased their likelihood of discussing new treatments, yet the impact of more abstract measures of quality of life, including psychological & emotional health as well as social functioning & personal goal fulfillment, are more difficult to quantify and are therefore less likely to be confidently discussed by genetic counselors with prospective parents.

A comparison between general responses to the 2013 and 2020 studies is outlined in Table 10 and illustrates the increased awareness of targeted treatments for CF over the past several years. In the intervening 7 years, significantly more genetic counselors have become aware of modulator therapies and have less concerns about instilling false hope when discussing them with patients. This change may suggest that counselors trust more long-term safety and efficacy data and are thus more comfortable in managing the expectations of prospective parents when discussing treatments. Nevertheless, there is a continuous trend of very few counselors having an in-depth knowledge of modulator therapies, even in 2020 when the majority of genetic counselors are aware that such therapies exist. This finding, in consideration with the fact that almost all counselors who participated in this study (98.11%) had heard of CFTR modulator therapies, yet only half (50.94%) would bring up the name of Trikafta (elx/tez/iva) to prenatal patients, suggests that counselors must have a sound understanding of newly approved therapeutics in order for them to discuss said therapeutics with prospective parents.

<b>Data from 2013 (Elsas, 2017)</b>	<b>Data from 2020</b>
Most (80%) initially reported they had never heard of Kalydeco (iva) or they were not sure exactly what it was.	Most (98.11%) initially reported they had already heard of CFTR modulators.
2.6% report knowing ‘quite a bit’ about CFTR modulators.	5.66% report knowing ‘quite a bit’ about CFTR modulators.
~65% of counselors were concerned that by discussing the Kalydeco (iva), they may instill false hope in their patients	1.89% of counselors were concerned that by discussing Trikafta (elx/tez/iva) they may instill false hope in their patients

Table 10: Comparison of responses to the same questions in the 2013 survey and the 2020 survey

Elsas et al. (2017) pointed out that there was a need for counselors to incorporate discussions of new treatment options in their sessions in 2017 and proposed that education of counselors about these options could be accomplished through future sessions at NSGC

conferences. At the 2020 NSGC Annual Educational Conference, Gunnar Esiason, a patient advocate with CF, gave a plenary lecture on his experience with CF and becoming eligible for Trikafta (elx/tez/iva). As a result, a question was added to this survey to gauge how many prenatal genetic counselors heard of Trikafta (elx/tez/iva) for the first time during his lecture. Of this study's participants, 9.43% reported they heard of Trikafta (elx/tez/iva) for the first time during Gunnar Esiason's lecture, thus contributing to the majority of participants knowing about CFTR modulators prior to taking this survey.

Participants' responses about their likelihood to discuss the impact of Trikafta on an affected individual's life expectancy, physical health, psychological and emotional health, social functioning and personal goal fulfillment, and child's daily care suggest that counselors would be most confident in Trikafta (elx/tez/iva) having visceral health impacts. They would be more likely to discuss the drug in the context of those visceral impacts rather than in the context of psychosocial impacts. Most (68%) were likely to discuss Trikafta having a "profound" and "significant" impact on physical health and the majority (60-70%) said they were likely to discuss Trikafta having "little to no" or "some" impact on psychological & emotional health and social functioning & personal goal fulfillment. Likelihood to discuss Trikafta having an impact on a child's daily care and life expectancy were more variable.

These responses aligned with the strength of correlations between counselor's perceived impact of CF on and the likelihood of discussing the impact that Trikafta (elx/tez/iva) would have on the 5 categories of quality of life. In order from strongest to weakest, correlations for each category are: physical health, child's daily care, life expectancy, psychological & emotional health, and social functioning & personal goal fulfillment.

Comparatively, counselors were generally more likely to discuss the impact of CF on lifestyle measures rather than on longevity and the more difficult to quantify social/personal features of life. The ranking of correlations between counselors' perceived impact of CF and their likelihood of discussing that impact for each category from strongest to weakest were: child's daily care, physical health, psychological and emotional health, life expectancy, social functioning & personal goal fulfillment. The strength of these correlations between counselors' perceived impact of CF and their likelihood of discussing the impact of the condition itself were stronger than those found between counselors' perceived impact of CF on and the likelihood of discussing the impact of Trikafta (elx/tez/iva). This change in strength of correlation and change in order of quality of life category indicates a difference in genetic counselor's approach to counseling a diagnosis versus counseling of the possible treatment for said diagnosis.

Counselors' tendency to discuss the physical effects of Trikafta (elx/tez/iva) and CF rather than the more subjective effects illustrate the continuity of behaviors observed in by Elsas et al. (2017). They noted that the absence of metrics which demonstrate the drug's ability to impact psychological wellbeing could make counselors hesitate to raise the issues. Many patient accounts praising the psychosocial impact of Trikafta (elx/tez/iva), including Gunnar Esiason's lecture, have circulated since the approval of the drug, yet there are no validated studies of its direct psychological, emotional, or social impact.

This discomfort to discuss all potential impacts of Trikafta (elx/tez/iva) with prenatal patients could be attributed to the varied perspectives genetic counselors have on how to best or who to best discuss newly approved therapies with prenatal patients. Relatedly, when counselors were questioned about their likelihood of discussing treatments for other conditions with prenatal patients, counselors were most likely to share information about early intervention programs for

children with developmental delays or disabilities and fetal surgery options. They were least likely to share information about current studies involving investigational therapies that are enrolling individuals with a particular genetic condition. The implication of this finding is that genetic counselors are more comfortable with treatment information that has been tested over time or is most imminent in effect and consequently see this sort of information as having greater benefit in the prenatal space. Interestingly, more counselors (79.25%) were likely to discuss successful cases of gene therapies used for genetic conditions such as SMA and sickle cell disease than were likely to bring up the name of Trikafta (elx/tez/iva) (50.94%) in a prenatal session. This finding may indicate that counselors view genetic conditions such as SMA and sickle cell disease as more severe or as having less treatment alternatives than cystic fibrosis.

Notably, counselors agreed that information about Trikafta (elx/tez/iva) would affect pregnancy management decisions, but they were not confident discussing Trikafta (elx/tez/iva) with prenatal patients. This disconnect between counselors' beliefs and actions could be attributed to the counselors' disagreement on who would be the most appropriate to discuss Trikafta (elx/tez/iva) with prenatal patients. The majority (99.11%) of counselors reported that it was important for prenatal genetic counselors to know about treatment options for CF. However, most counselors (83.02%) believed information regarding Trikafta (elx/tez/iva) would be best explained by a pediatric pulmonologist or other CF expert. This belief does not align with the timeline of events involved in a diagnosis of CF because most patients will make pregnancy management decisions before ever meeting a CF specialist if potential treatments are not brought up prenatally. This has implications for future practice by illustrating the need for a practitioner with expertise in discussing targeted treatments to be stationed within the prenatal setting so that potential parents can make the most informed decisions while managing their pregnancies.

Despite the lack of confidence genetic counselors have in discussing Trikafta (elx/tez/iva) with prenatal patients, more counselors agreed they would discuss treatment availability if the treatment is available by age 2 at the time the infant is expected rather than if the treatment is available to those age 6 and older at the time the infant is expected. The greater likelihood of counselors to discuss treatments with younger ages of eligibility suggests that prenatal counselors are more comfortable in bringing up topics that may prove to have more of an imminent effect on the potential infant's life. Consequently, counselors' likelihood to discuss Trikafta (elx/tez/iva) with prenatal patients may increase as the age of eligibility expands from 12 years and older towards infancy.

### **Limitations**

This project is limited in several ways. Of note, not all couples who receive a prenatal diagnosis of CF receive genetic counseling, so these data are not representative of all experiences. Additionally, this project did not survey prospective parents, so these data cannot be used to explore how genetic counselors influence the decision-making process of a couple facing a prenatal diagnosis.

Question 20 was phrased as "Who do you feel is the most appropriate individual to discuss Trikafta (ELX/TEZ/IVA) with patients?" without distinguishing 'patients' as 'prenatal patients'. This makes the responses likely to be applicable to all patients diagnosed with CF rather than the specific grouping of prenatal patients that are the focus of this study.

The response rate of only 6.12% from the 866 person NSGC Prenatal SIG reduces the generalizability of these findings. Additionally, this low response rate may indicate participation bias because the recruitment message includes mention of CF and consequently, members of the

Prenatal SIG who have a particular interest in CF or significant background knowledge may have been more likely to take the survey.

This low response rate may also reflect the survey fatigue of genetic counselors because members of the profession are often asked to participate in studies through weekly emails from the NSGC. The 14 participants, who did not complete the full survey, began skipping questions as the question style shifted from gathering demographic information towards gathering opinions. The most significant drop in responses came after the educational intervention, between questions 17 and 18, with a consistent decline as the length and complexity of questions progressed. This midway drop may indicate further survey fatigue due to a high volume of text within the survey body and repeated Likert-scale question style.

### **Future directions**

Prenatal providers would benefit from guidelines about who should discuss emerging treatments with potential parents and how to best facilitate those conversations. Genetic counselors do not see every couple experiencing a prenatal diagnosis, so a collaborative approach to developing these guidelines between organizations including patient advocacy groups like the Cystic Fibrosis Foundation, the American College of Obstetrics and Gynecology, and the NSGC would be beneficial. These guidelines would help to more clearly define the role of a prenatal genetic counselor and ensure patients experiencing the same sort of diagnosis receive the same quality of care. More attention to educating genetic counselors about new treatments could also be paid. Counselors reported that they currently learn about new treatments most often from lectures and conferences (100%), colleagues (77.36%), and professional practice guidelines (54.72%) (Chart 7). Therefore, increasing the robustness, relevance, and actionability of the information

about emerging treatments at lectures and encouraging the circulation of that information would contribute to genetic counselors' awareness of new therapeutics.

The preliminary data gathered here, in continuation of the analysis done by Elsas et al. (2017), indicate that exploration of patient perspectives on how genetic counselors influence the decision-making process of a couple facing a prenatal diagnosis is necessary. Additionally, assessment of which couples who receive a prenatal diagnosis of CF receive genetic counseling and why would contribute to a better understanding of how genetic counselors can support prenatal patients. Finally, data indicating that age of eligibility impacts counselors' likelihood of discussing treatments with prenatal patients suggests that research is needed to explore what phases of life prenatal counselors feel comfortable counseling on.

### **CONCLUSION**

The 2019 FDA approval of Trikafta (elx/tez/iva) marked a major milestone in the treatment of cystic fibrosis by expanding eligibility for modulator therapies to all individuals 12 years and older who are heterozygous for the F580del variant. This approval sparked the need to revisit the question raised by Elsas et al. in the 2017 study that launched after the approval of Kalydeco (iva). They explored the attitudes of prenatal genetic counselors toward discussion of approved and experimental treatments for cystic fibrosis and how knowledge of those treatments influenced their practice under. This study made the same inquiry while accounting for changed circumstances including the approval of new drugs, continued advancement of CF care, and evolution of genetic counseling practice.

It was found that prenatal genetic counselors believe it is important for prenatal genetic counselors to know about treatment options for CF, yet their opinions vary on how to best utilize that knowledge. As targeted, genotype specific, modulators become the standard of care for

individuals with CF, it is becoming increasingly relevant for genetic counselors to have the ability to counsel patients on their eligibility for life changing treatment. Nevertheless, the level on which counselors are likely to share information about treatment varies, especially when it comes to discussing potential treatment impact on subjective measures of quality of life. There are no guidelines for how to best share treatment information with prenatal patients and no consensus on the role of prenatal genetic counselors in discussing treatment options with patients. This illustrates that there is an opportunity for multidisciplinary collaboration to develop materials for clinical guidance within the reproductive genetics arena as well as for development of precise definitions of specialty roles within the genetic counseling field.

**FIGURES**

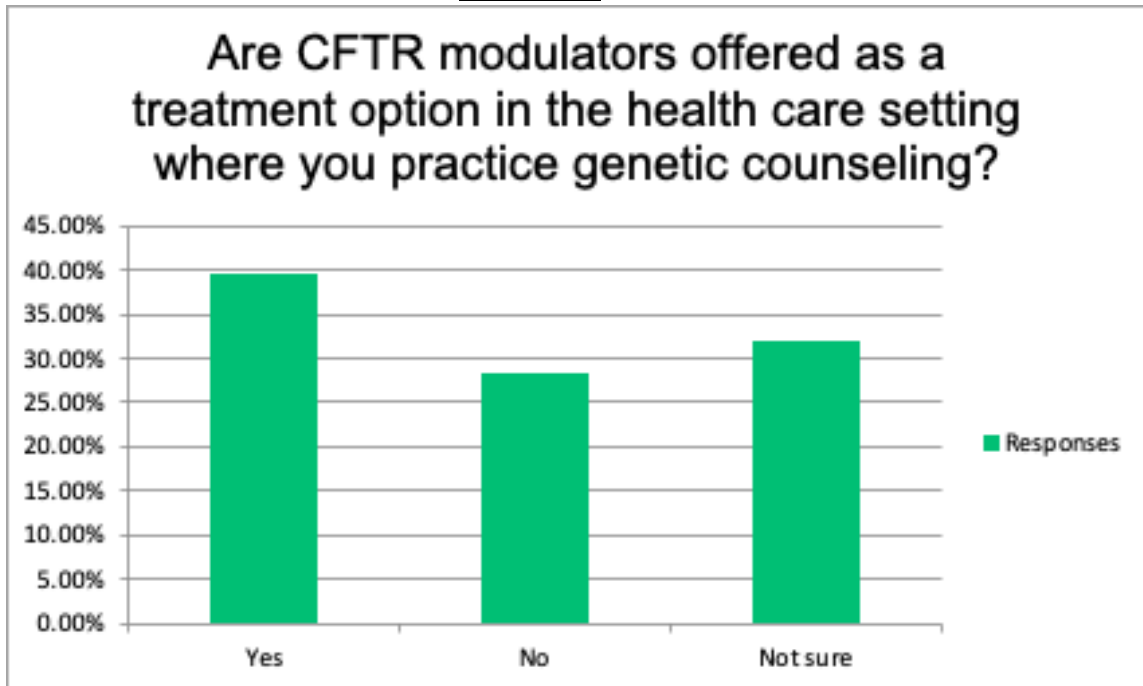


Chart 5: Question 14

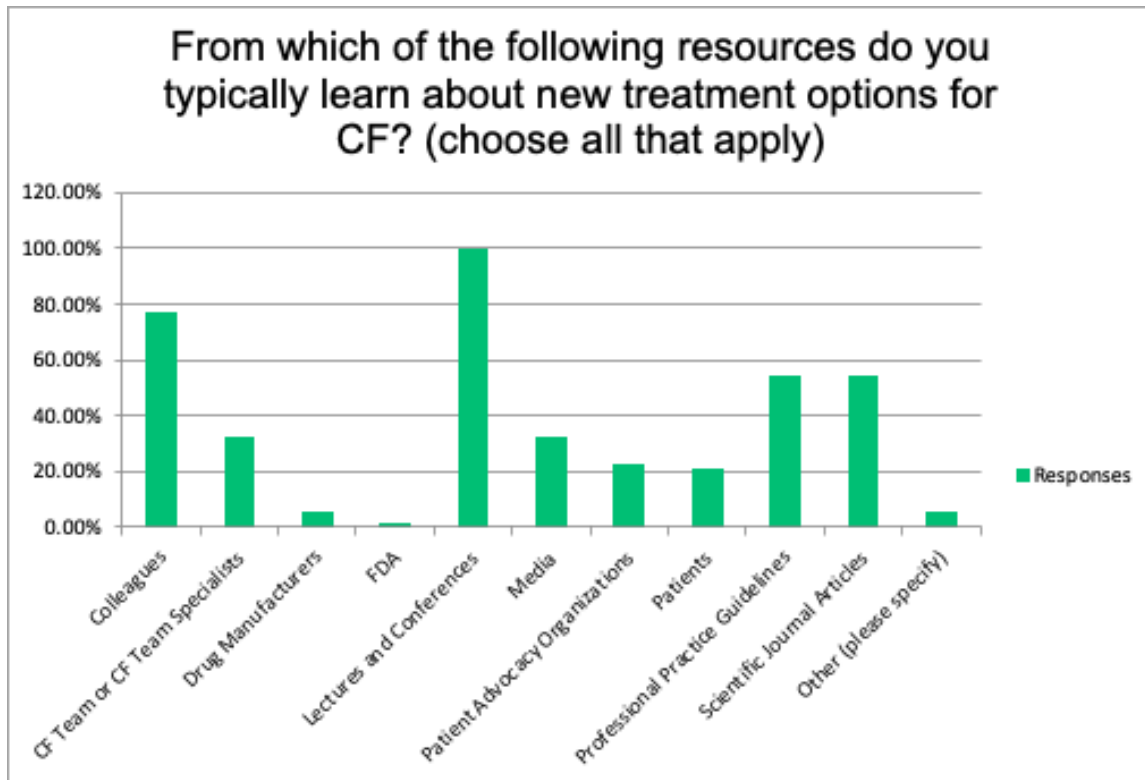


Chart 7: Question 16. Other responses include: Prenatal SIG Webinars & ListServ, I teach a course in which this material is discussed, and I have a close friend with CF

## REFERENCES

1. Andersen, D. H. (1938). Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *American journal of Diseases of Children*, 56(2), 344-399.
2. Beeson, D., & Golbus, M. S. (1979). Anxiety engendered by amniocentesis. *Birth defects original article series*, 15(5C), 191-197.
3. Bobadilla, J. L., Macek Jr, M., Fine, J. P., & Farrell, P. M. (2002). Cystic fibrosis: a worldwide analysis of CFTR mutations—correlation with incidence data and application to screening. *Human mutation*, 19(6), 575-606.
4. Castellani, C., Macek Jr, M., Cassiman, J. J., Duff, A., Massie, J., Leo, P., ... & Cuppens, H. (2010). Benchmarks for cystic fibrosis carrier screening: a European consensus document. *Journal of Cystic Fibrosis*, 9(3), 165-178.
5. CFTR2@JohnsHopkins - home page. (n.d.). Retrieved February 19, 2021, from <https://cftr2.org/>
6. Clancy, J. P., Cotton, C. U., Donaldson, S. H., Solomon, G. M., VanDevanter, D. R., Boyle, M. P., ... & Tuggle, K. L. (2019). CFTR modulator theratyping: current status, gaps and future directions. *Journal of Cystic Fibrosis*, 18(1), 22-34.
7. Clancy, J. P. (2018). Rapid therapeutic advances in CFTR modulator science. *Pediatric pulmonology*, 53(S3), S4-S11.

8. Collins, Francis S. "Cystic fibrosis: molecular biology and therapeutic implications." *Science* 256.5058 (1992): 774-779.
9. Cutting, G. R. (2015). Cystic fibrosis genetics: from molecular understanding to clinical application. *Nature Reviews Genetics*, 16(1), 45-56.
10. Cystic Fibrosis Foundation Patient Registry. (2020). *2019 Patient Registry Snapshot*. Retrieved February 19, 2021, from <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Cystic-Fibrosis-Foundation-Patient-Registry-Snapshot/>.
11. Cystic Fibrosis Foundation Patient Registry. (2019). *2018 Patient Registry Annual Data Report*. Retrieved February 19, 2021, from <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf>
12. Dorfman, R., & CFTR1 Team. (2011). Cystic fibrosis mutation database [Internet].
13. Elsas, C. R., Schwind, E. L., Hercher, L., Smith, M. J., & Young, K. G. (2017). Attitudes toward discussing approved and investigational treatments for cystic fibrosis in prenatal genetic counseling practice. *Journal of genetic counseling*, 26(1), 63-71.
14. Farrell, P. M., White, T. B., Ren, C. L., Hempstead, S. E., Accurso, F., Derichs, N., ... & Sosnay, P. R. (2017). Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *The Journal of pediatrics*, 181, S4-S15.
15. Farrell, P. M., White, T. B., Howenstine, M. S., Munck, A., Parad, R. B., Rosenfeld, M., ... & McColley, S. A. (2017). Diagnosis of cystic fibrosis in screened populations. *The Journal of pediatrics*, 181, S33-S44.
16. FDA approves KALYDECO™ (IVACAFTOR), the first medicine to treat the underlying cause of cystic fibrosis. (2012, January 31). Retrieved February 19, 2021, from <https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecotm-ivacaftor-first-medicine-treat>
17. FDA approves new breakthrough therapy for cystic fibrosis. (2019, October 21). Retrieved February 19, 2021, from <https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis>
18. Foil, K. E., Powers, A., Raraigh, K. S., Wallis, K., Southern, K. W., & Salinas, D. (2019). The increasing challenge of genetic counseling for cystic fibrosis. *Journal of Cystic Fibrosis*, 18(2), 167-174.
19. Heijerman, H. G., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., ... & Majoor, C. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*, 394(10212), 1940-1948.
20. Hill, M., Twiss, P., Verhoef, T. I., Drury, S., McKay, F., Mason, S., ... & Chitty, L. S. (2015). Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences and cost analysis. *Prenatal diagnosis*, 35(10), 950-958.

21. Kessels, S. J., Carter, D., Ellery, B., Newton, S., & Merlin, T. L. (2020). Prenatal genetic testing for cystic fibrosis: a systematic review of clinical effectiveness and an ethics review. *Genetics in Medicine*, 22(2), 258-267.
22. Means, C., Cirino, A., Swenson, K. B., & Austin, J. (2020). I am a Genetic Counselor”: A qualitative exploration of field leaders’ perceptions of the title “genetic counselor. *Journal of genetic counseling*, 29(1), 97-104.
23. Michie, S., Dormandy, E., & Marteau, T. M. (2003). Informed choice: understanding knowledge in the context of screening uptake. *Patient Education and Counseling*, 50(3), 247-253.
24. Middleton, P. G., Mall, M. A., Dřevínek, P., Lands, L. C., McKone, E. F., Polineni, D., ... & Jain, R. (2019). Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine*, 381(19), 1809-1819.
25. National Society of Genetic Counselors’ Definition Task Force [Resta R, Biesecker BB, Bennett R.L., Blum S, Hahn S.E., Strecker M.N., Williams J.L (2006). A new definition of genetic counseling: National Society of genetic counselors’ task force report. *Journal of Genetic Counseling*, 15(2), 77–83.
26. Quittner, A. L., Buu, A., Messer, M. A., Modi, A. C., & Watrous, M. (2005). Development and validation of the cystic fibrosis questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest*, 128(4), 2347–2354.
27. Ridley, K., & Condren, M. (2020). Elexacaftor-Tezacaftor-Ivacaftor: The First Triple-Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulating Therapy. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*, 25(3), 192–197. <https://doi-org.remote.slc.edu/10.5863/1551-6776-25.3.192>
28. Schrijver, Iris, et al. "The spectrum of CFTR variants in nonwhite cystic fibrosis patients: implications for molecular diagnostic testing." *The Journal of Molecular Diagnostics* 18.1 (2016): 39-50
29. Stern, A. M. (2012). *Telling genes: the story of genetic counseling in America*. JHU Press.
30. Taylor-Cousar, J. L., Mall, M. A., Ramsey, B. W., McKone, E. F., Tullis, E., Marigowda, G., ... & Rowe, S. M. (2019). Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. *ERJ open research*, 5(2).
31. Vertex Pharmaceuticals. (2020). *TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor; ivacaftor) Tablets FULL PRESCRIBING INFORMATION* [Brochure]. Boston, MA: Author. Retrieved January 1, 2021, from [https://pi.vrtx.com/files/uspi\\_elexacaftor\\_tezacaftor\\_ivacaftor.pdf](https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf)
32. Zeevi, D. A., Zahdeh, F., Kling, Y., Rosen, T., Renbaum, P., Ron-El, R., ... & Altarescu, G. (2018). Noninvasive paternal exclusion testing for cystic fibrosis in the first five to eight weeks of gestation. *Scientific reports*, 8(1), 1-9.

APPENDIX  
Appendix A - Survey

## Inclusion Criteria

2. Are you an American Board of Genetic Counseling (ABGC) board-certified or board-eligible genetic counselor?

Yes

No

3. Do you provide prenatal or preconception genetic counseling services to patients in the United States?

Yes

No

---

## Cystic Fibrosis Overview

Cystic fibrosis (CF) is a multisystem genetic condition characterized by progressive lung disease, chronic lung infections, and pancreatic insufficiency. National registry data predicts that of babies born with CF in 2018, half are projected to live to 47 years or older. Life expectancy has steadily increased associated with new treatment modalities and quality improvement efforts.

CF is caused by recessive variants in the cystic fibrosis transmembrane regulator (CFTR) gene which leads to dysfunction of the CFTR protein. There are more than 2,000 known CFTR variants, though the pathogenic significance of most has not been fully described. The F508del is the most common pathogenic variant. The pathogenic significance of CFTR variants can be found at [www.cftr2.org](http://www.cftr2.org).

The CFTR protein transports chloride ions (a component of salt) in and out of cells which helps to regulate the flow of water in tissues. Without the movement of chloride ions mucus in various organs becomes thick and sticky and sweat becomes abnormally salty. The signs and symptoms of CF are caused by this thick mucus. For example, it clogs airways in the lungs, traps bacteria, and obstructs the pancreas' release of digestive enzymes.

Most people with CF in the United States receive treatment at Cystic Fibrosis Foundation accredited CF Centers. Multidisciplinary teams evaluate and recommend testing and treatment from the newborn period to adulthood.

## Demographic Information

4. How many years have you been practicing as a prenatal genetic counselor?

- < 1 year                       10-14 years
- 1-4 years                         15-20 years
- 5-9 years                          20+ years

5. What best describes your work environment

- Diagnostic Laboratory                       Private Hospital
- Private Practice                               Telehealth company
- Public Hospital                                 University Hospital
- Other (please specify)

6. How many prenatal CF diagnoses do you see in a year?

- 0-1
- 2-5
- 6-9
- 10+

**7. Do you have any specialized experience in or knowledge of CF?**

- No
- Yes, I work at/have worked at a CF clinic
- Yes, I have personal/familial experience with CF
- Yes, other

**8. Do you work at an institution that is formally associated with an accredited CF center?**

- Yes
- No

**9. When a prenatal CF diagnosis is made, do you refer to or recommend one or more accredited CF centers?**

- Always
- Never
- Sometimes (please describe)



## Scenario 1

A couple is referred to you after prenatal diagnosis reveals that their pregnancy carries two pathogenic *CFTR* variants and will be affected by classic cystic fibrosis (CF).

10. Estimate the impact that CF will have on the following:

	Little to no impact	Some impact	Significant impact	Profound impact
Life Expectancy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Physical Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychological and Emotional Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Social Functioning and Personal Goal Fulfillment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Child's Daily Care	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

11. In counseling the couple, would you plan to address the impact of CF on the following:

	Definitely	Probably	Probably Not	Definitely Not
Life Expectancy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Physical Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychological and Emotional Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Social Functioning and Personal Goal Fulfillment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Child's Daily Care	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

12. Have you heard of the class of drugs called CFTR modulators? Examples are elexacaftor/tezacaftor/ivacaftor (Trikafta™), ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi®), and tezacaftor/ivacaftor (Symdeko®).

- No, I've never heard of them
- Yes, I've heard of them but I'm not sure exactly what they are
- Yes, I know a little bit about them
- Yes, I know quite a bit about them

13. Did you first hear of Trikafta (ELX/TEZ/IVA) at Gunnar Esiason's talk at the 2020 NSGC Annual Conference?

- Yes
  - No
-

14. Are *CFTR* modulators offered as a treatment option in the health care setting where you practice genetic counseling?

- Yes
- No
- Not sure

15. How important do you feel it is for prenatal genetic counselors to know about treatment options for CF?

- Extremely important
- Very important
- Somewhat important
- Not so important
- Not at all important
- Only important for those counseling at a CF center
- Only important for those counseling a family after the birth of an affected child

16. From which of the following resources do you typically learn about new treatment options for CF? (choose all that apply)

- Colleagues
- CF Team or CF Team Specialists
- Drug Manufacturers
- FDA
- Lectures and Conferences
- Other (please specify)
- Media
- Patient Advocacy Organizations
- Patients
- Professional Practice Guidelines
- Scientific Journal Articles

17. Do you generally discuss improving treatment options for CF with patients?

Yes

No

---

## Scenario 2

A couple is referred to you after prenatal diagnosis reveals that their pregnancy carries two pathogenic *CFTR* variants and will be affected by classic cystic fibrosis (CF).

The genotype includes at least one copy of F508del.

18. Would you plan to address the impact of Trikafta (ELX/TEZ/IVA) on the following:

	Little to no impact	Some impact	Significant impact	Profound impact
Life Expectancy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Physical Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychological and Emotional Health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Social Functioning and Personal Goal Fulfillment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Child's Daily Care	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

19. Regarding Trikafta (ELX/TEZ/IVA) , how likely are you to share the following with the patients?

	Extremely likely	Somewhat likely	Neither likely nor unlikely	Somewhat unlikely	Extremely unlikely
The name of the drug	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The molecular basis of the drug	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Expected benefits of treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Side affects of treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cost of the drug/insurance coverage	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Current availability of the drug to those 12 years and older	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Referral to a specialist	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

20. To what extent do you agree or disagree with the following statements:

	Strongly Disagree	Disagree	Neither Disagree nor Agree	Agree	Strongly Agree
Information about Trikafta (ELX/TEZ/IVA) would affect pregnancy management decisions.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The benefits of Trikafta (ELX/TEZ/IVA) justify any costs and risks of this treatment.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I am uncomfortable discussing Trikafta (ELX/TEZ/IVA) given the lack of long term data.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I am comfortable discussing Kalydeco (IVA) and Orkambi (LUM/IVA) with prenatal patients because they have long term data.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I would discuss treatment availability if the treatment is available by age 2 at the time the infant is expected.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I would discuss treatment availability if the treatment is available to those age 6 and older at the time the infant is expected.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

	Strongly Disagree	Disagree	Neither Disagree nor Agree	Agree	Strongly Agree
I would discuss treatment availability if the treatment is available to those age 12 and older at the time the infant is expected.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
By discussing Trikafta (ELX/TEZ/IVA) with prenatal patients I would be instilling false hope.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I know where to find information about Trikafta (ELX/TEZ/IVA) and other new treatment options.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel confident discussing Trikafta (ELX/TEZ/IVA) with prenatal patients.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
It is important for professional organizations to provide guidelines on how and when to discuss Trikafta (ELX/TEZ/IVA) in practice.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

---

21. Who do you feel is the most appropriate individual to discuss Trikafta (ELX/TEZ/IVA) with patients?

- Geneticist
  - Maternal-Fetal Medicine Specialist
  - Obstetrician
  - Patient advocacy group representative
  - Other (please specify)
- Pediatric genetic counselor
  - Pediatrician
  - Pediatric Pulmonologist or other CF expert
  - Prenatal genetic counselor

22. Would you typically share the following information prenatal patients when applicable? (check all that apply)

- Discussion of successful cases of gene therapies used for genetic conditions such as SMA and sickle cell disease
- Current studies involving investigational therapies that are enrolling individuals with a particular genetic condition
- Treatment modalities such as physical and/or occupational therapy for disorders limiting physical abilities
- Dietary management for metabolic conditions
- Fetal surgery options in the case of neural tube defects
- Early intervention programs for children with developmental delays or disabilities

## Appendix B – Recruitment Message

### **Exploring Attitudes Towards Newly Approved Therapeutics in Prenatal Genetic Counseling Practice**

You are invited to participate in a research study exploring how genetic counselors' knowledge of cystic fibrosis therapies may influence prenatal practices. This study has been reviewed by the Sarah Lawrence College IRB and determined to be EXEMPT. Funding for this project was provided by the National Society of Genetic Counselors CF and CFTR Spectrum Special Interest Group. The survey takes approximately 8-10 minutes to complete.

Please contact Charlotte Close ([cclose@gm.slc.edu](mailto:cclose@gm.slc.edu)) at the Joan H. Marks Graduate Program in Human Genetics via email if you have any questions about taking part in this study.

## Appendix C – Consent Form

Investigator:

Charlotte Close: [cclose@gm.slc.edu](mailto:cclose@gm.slc.edu)

45 Wrexham Rd

Bronxville, New York 10708

I am asking you to take part in a research study at Sarah Lawrence College. Please read through the following questions and responses and ask any other questions that will help you to decide whether or not to participate.

What is the purpose of this study?

- The overall purpose of the study is to explore what prenatal genetic counselors currently know about targeted therapeutics for CF, and how subsequent education about those therapeutics will impact their counseling of a prenatal diagnosis of CF.

Why am I being asked to participate?

- All board-certified genetic counselors currently practicing in a prenatal setting are eligible

What will I be asked to do?

- The study is designed to collect data through an online survey. The survey will lead participants through a variety of clinical scenarios, an educational intervention, and follow-up questions.
- This survey takes an estimated 10 minutes to complete.

Is my participation voluntary?

- Yes, participants can choose to opt out of the study at any point and doing so will not affect their relationship with Sarah Lawrence College.
- Participants can choose not to answer specific questions without having to justify their choice.

Are there any benefits or risks associated with my participation in this study?

- There are no direct benefits associated with participation in this study.
- The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Will I be compensated for my participation?

- Participants will not be compensated

Will the information I provide be kept confidential?

- Participants will not be identified in any written or oral report of the research study.
- Every reasonable effort will be made to keep data secure and confidential; however, the degree to which this is possible is determined by the technology being used. This survey excludes all respondent information including first name, last name, email address, IP address, and custom data from your results. SurveyMonkey records respondent IP addresses in backend logs and deletes them after 13 months.

If I have any questions or concerns after the study, how can I contact you?

Investigator

Charlotte Close  
cclose@gm.sl.c.edu  
(847) 612 – 7575

Advisor

Chantal Duteau Buck MS, CGC  
cduteau@sarahlawrence.edu

Who can I contact if I have questions about my rights as a research participant?

- The IRB co-chairs Professors Elizabeth Johnston (203-722-3287) and Claire Davis (914-395-2605) at [irb@sarahlawrence.edu](mailto:irb@sarahlawrence.edu).

## **Appendix D- CFTR Modulator Information**

Please review the following information about cystic fibrosis transmembrane conductance regulator (CFTR) modulators before answering the following questions. This information was obtained from each of the drugs' clinical brochures, clinical trial literature, and the CFF 2018 Patient Registry Annual Data Report.

CFTR modulators are a group of FDA-approved drugs used to treat cystic fibrosis. These drugs target and correct the specific defects in the gated membrane channel protein that cause CF. Each drug targets a specific type of defect, consequently, only individuals carrying the genetic variants causing those defects are eligible. Currently available drugs are dosed orally, every four hours

These drugs are not a cure and are prescribed in conjunction with traditional treatment regimens.

	<b>Kalydeco (IVA)</b>	<b>Orkambi (LUM/IVA)</b>	<b>Symdeko (TEZ/IVA)</b>	<b>Trikafta (ELX/TEZ/IVA)</b>
<b>Current age of Eligibility (as of November 2020)</b>	4 months and older	2 years and older	6 years and older	12 years and older
<b>CFTR Variants Approved for Treatment</b>	38 <sup>+</sup> gating, conduction, splice site and residual function	Two copies of the F508del variant	Two copies of the F508del variant	At least one copy of the F508del variant
<b>Percent of CF population eligible based on CFTR variant</b>	15%	44.2%	44.2%	90%
<b>Class of drug*</b>	Potentiator	Corrector and potentiator	Corrector and potentiator	Two correctors and a potentiator
<b>Benefits</b>	Significant improvement in pulmonary function tests, significant reduction of pulmonary exacerbations, improvements in body weight gain, normalization of sweat chloride levels	Improvement in pulmonary function tests, significant reduction of pulmonary exacerbations	Improvement in pulmonary function tests, significant reduction of pulmonary exacerbations	Significant improvement in pulmonary function tests, significant reduction of pulmonary exacerbations, higher patient reported quality of life, normalization of sweat chloride levels
<b>Serious Adverse Reactions</b>	Abdominal pain  Increased hepatic enzymes = increased liver enzymes  Hypoglycemia = low blood sugar	Pneumonia  Hemoptysis = coughing up blood  Cough  Increased blood creatine phosphokinase = increased enzymes indicating muscle damage  Transaminase elevations = increased liver enzymes	Distal intestinal obstruction syndrome	Rash and influenza
<b>Other Possible Side Affects</b>	In the eyes, opacities of the lens that are non – congenital have been reported			
<b>Annual Anticipated Cost</b>	\$311,000 per patient per year	\$272,000 per patient per year	\$292,000 per patient per year	\$311,503 per patient per year

\*Potentiators: hold the gate in the CFTR protein open so that chloride ions can flow through the cell membrane.

\*Correctors: help the CFTR protein form the right shape and be trafficked the cell surface.

+

2789+5G→A	D110H	F1052V	G551S	R117H	S549R
3272-26A→G	D1152H	F1074L	K1060T	R347H	S945L
3849+10kBc→T	D1270N	G1069R	L206W	R352Q	S977F
711+3A→G	D579G	G1244E	P67L	R74W	
A1067T	E193K	G1349D	R1070Q	S1251N	
A455E	E56K	G178R	R1070W	S1255P	
D110E	E831X	G551D	R117C	S549N	

---