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Infertility Education for Men With Cystic Fibrosis and Its Effects: Outlooks on Fertility and Birth Control

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INFERTILITY EDUCATION FOR MEN WITH CYSTIC FIBROSIS AND ITS EFFECTS: OUTLOOKS ON FERTILITY AND BIRTH CONTROL

By

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ABSTRACT

Many men with Cystic Fibrosis (CF) are infertile; however, few studies have evaluated fertility outlook of men with CF since the advent of modulator therapy. As predicted survival and quality of life improve, family planning is an area of increased interest for the CF community. The current study surveyed men with CF to explore their outlook on fertility, family planning, and birth control use with the option to receive a home fertility test and follow-up interview with study staff.

Seventy-five men with CF completed the survey and 53 (71%) believed they were likely infertile. Most recalled learning about infertility between age 10-20 years and from a healthcare provider. Forty participants (53%) reported a previous clinical sperm count, with 27 (68%) reporting infertility. Four participants completed at-home fertility tests, all of which were negative. These participants found home testing valuable and easy to complete.

Seventeen participants (23%) indicated they had a child through various means: biological, donor conceived, adopted, or stepchild. Most participants (65%) indicated they wanted a child in the future. Men who have taken modulators were significantly more likely to desire a child in the future than those who have not (77% versus 53%), and to feel that they would enjoy parenting a child (87% versus 67%).

Using condoms for pregnancy and/or sexually transmitted infection prevention at any time was reported by most heterosexual participants (52/70, 74%). However, some participants (39/70, 56%) reported not feeling obligated to use birth control due to the likelihood of infertility.

Rates of known or assumed CF related male infertility are lower in this cohort than expected. Our findings highlight opportunities for improved fertility education including family building options, safe sex practices, and access to semen analysis. Preliminary data support potential utility of home semen analysis, which should be explored further in future research.

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BACKGROUND

Cystic Fibrosis (CF) remains one of the most commonly diagnosed recessive genetic disorders in the United States (Scotet et al., 2020). Although previously lethal in childhood, many more individuals are living into their adult years, with a median predicted survival of 59 years in 2020 (Cystic Fibrosis Foundation [CFF], 2021). This is a striking improvement over previous decades and represents the fruition of lifetime work and advocacy of many researchers, doctors, healthcare professionals and families. As the medical world has developed more effective methods of treating the most significant morbidities associated with CF and treatments to address the underlying genetic causes of CF, people with CF are able to achieve numerous lifetime goals. For men with CF who desire to become a father, accomplishing this goal may be complicated, as many men with CF experience infertility (McBride et al., 2021). Although assisted reproductive technology may allow some males with infertility to father pregnancies, barriers may exist between men with CF and access to optimal fertility counseling and testing. Our research aimed to understand the outlook on fertility, family planning, birth control, and contributing factors for men with CF.

1.1 Cystic Fibrosis

CF is a complex, multisystem disease that affects the respiratory, digestive, reproductive, and other systems. CF is a single gene, autosomal recessive disorder first described in 1938. The birth incidence of CF has been recently reported to be 1 in 4,000 in the US population, though incidence varies significantly among ethnic groups and is highest in those of Northern European descent (Scotet et al., 2020). In 1989, the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene was discovered and the most common *CFTR* variant- F508del- was described in addition to other variants that were thought to convey residual function in some body systems (Kerem et al., 1989). People affected by CF experience negative effects caused by a thick mucus lining in these tissues which is typically controlled by the body via chloride transport across epithelial cell membranes via the CFTR protein. When chloride is transported across the cell membrane, water molecules also move across the cell membrane in the same direction by way of diffusion or osmosis. Therefore, the CFTR protein also plays an integral role in fluid secretion.

1.1.1 Lung Manifestations

Lung disease is one of the most burdensome symptoms of CF and is recognized as the most common cause of mortality in CF patients (Dinwiddie, 2000). Demise is often the last domino to fall in a chain of pulmonary events that originates from the basic defect in *CFTR*. The viscosity of the mucus lining in the lungs inhibits the function of cilia that are typically responsible for moving mucus up the respiratory tract. This mucus also traps bacteria and other pathogens

within the lungs, leading to recurrent infections and, secondarily, chronic lung inflammation. Together, these factors lead to drastically worsening lung function over a patient's lifetime. Commonly, individuals with CF experience a steep decline in lung function from ages 6 to 30 years which is followed by a long period of plateau (Earnest et al., 2020). However, this is variable between individuals, even among those with the same genotype.

Individuals affected by CF are offered a wide range of interventions to help ease pulmonary symptoms and often employ many of them in combination. Prophylactic antibiotics help to reduce the risk of bacterial colonization. In the case that a bacterial infection is diagnosed, oral, inhaled, and intravenous antibiotics are used as treatments. Airway clearance is also a main goal of treatment. Saline nebulizer treatments, breathing techniques, percussion therapy, and special medical devices that change the amount of air pressure inside the lungs are all utilized to clear mucus from the respiratory system. Individuals with CF and their caregivers often spend more than an hour of every day on airway clearance and nebulizer treatments (Johns Pool, 2019). As lung function diminishes, lung transplant is a surgical treatment option that is pursued by some patients with CF, but many obstacles exist.

1.1.2 Pancreatic Manifestations

The pancreas is also greatly impacted by CF. Typical pancreas function involves secreting digestive enzymes into the duodenum. Here, these enzymes work to break down nutrients in food. Because of the lack of water in the digestive secretions, pancreatic enzymes are three times the concentration and

much thicker in CF as they would be in an unaffected individual (Kelly and Buaxbaum, 2015). Thick secretions cause blockages in pancreatic ducts, which interfere with the enzymes exiting the pancreas. Instead, these enzymes build up within the pancreas and cause inflammation (Kelly and Buaxbaum, 2015). This progressive damage may lead to pancreatitis, pancreatic insufficiency, and CF related diabetes mellitus (CFRD). Pathogenicity within the pancreas is followed by several other possible complications along the digestive tract and related organs. Patients with CF also struggle with malabsorption, partially due to the lack of pancreatic enzyme to aid in digestion and partially due to the thick mucus lining in the intestines that makes absorption of nutrients inefficient (CFF). Achieving and maintaining a healthy weight can be difficult for many people affected by CF (CFF).

An appropriate diet is also a focus of CF management (Stallings et al., 2008). Nutritionists and dieticians are often specifically trained on the needs of patients with CF. Eating a diet that is high in protein, calories, and salt is often necessary for patients with CF to maintain their health (Stallings et al., 2008). Additionally, taking a calculated dose of pancreatic enzymes orally before every meal helps with absorption of the food that is consumed (Borowitz et al., 1995). Because intake needs can be so high, some individuals with CF will get a gastrostomy tube to make consuming enough calories more convenient.

1.1.3 Sweat Gland Manifestations

One of the earliest signs of CF recognized by parents of infants diagnosed with CF is often a salty taste when a baby is kissed. This can be striking as

individuals with CF have three to five times more salt in their sweat than people who do not have CF (Quinton, 2007). This is again due to the basic defect in *CFTR*. Sweat is typically secreted as a hypertonic solution of water and salt, and then partially reabsorbed to create a hypotonic solution. Sodium and chloride are reabsorbed with a small amount of water before sweat reaches the skin's surface. However, in CF, this cellular transport cannot take place as it should. This leads to high levels of salt being present on the skin's surface. This is one reason for dieticians recommending high levels of salt consumption for their patients. Replenishing lost salt is vital for maintaining electrolyte balance throughout the body. This pathognomonic sign of CF has also become one of the gold standards for diagnosis.

1.1.4 Reproductive Manifestations

CF affects fertility and reproduction in individuals of both sexes (Amaral et al., 2020). Although females typically have an intact reproductive tract, factors like secondary amenorrhea, generally poor health, and thick cervical mucus can make becoming pregnant and carrying a pregnancy to term difficult (Ahmed et al., 2013). However, more women with CF than ever are becoming mothers with advances in healthcare. Conversely, many males with CF are not fertile. Although they produce sperm, many males are born with a condition known as congenital bilateral absence of the vas deferens (CBAVD) (Barreto et al., 1991). CBAVD cannot typically be accurately diagnosed using a physical exam and is generally diagnosed using ultrasound, but surgical methods of diagnosis are equally reliable (Lin & Huang, 2020). The vas deferens is a duct that carries

sperm from the testis, where it is produced, to the urethra, where it can then exit the body. Without the vas deferens, natural conception is impossible. However, with advances in reproductive technology, sperm retrieval and intracellular insemination is now possible and allows men with CBAVD to become biological fathers (McBride et al., 2021).

Ultimately, CF is a disease that affects many different body systems and a person's quality of life. Some of these factors are difficult to measure, especially because changes in available treatments are happening so quickly. In 2020, the median predicted survival of a person with CF was 59 years (CFF, 2021). This represents a significant increase in life expectancy over the last several decades. Individuals with CF are living longer, creating new challenges to ensure that people in this community are living lives that they find personally fulfilling; for some, this includes becoming a parent.

1.2 Diagnosing Cystic Fibrosis

In the United States, all 50 states and the District of Columbia include CF on the newborn screening panel. Newborn screening is a panel of tests designed to detect treatable disorders that lead to serious health problems in childhood. To screen for CF, blood spots are used to test for high levels of immunoreactive trypsinogen (IRT). IRT is a protein that is produced in the pancreas and can be increased in a newborn for many reasons, not just the presence of CF. For this reason, this test is only considered a screening and must be followed by other tests in order to make a diagnosis of CF. In some cases of high IRT levels, a

genetic test will also be performed on the blood spot to detect common variants in *CFTR*.

There are over 2,000 known variants in *CFTR*. Sequencing and deletion/duplication analysis of the *CFTR* gene can be useful in diagnosis and predicting some phenotypic features of CF. However, the gold standard of diagnosis remains the Quantitative Pilocarpine Iontophoresis Sweat Test (sweat test) (Farrell et al., 2017). Any sweat test that is performed correctly and yields a result of 60 mmol/L or greater of chloride in sweat secretions is indicative of a CF diagnosis. Those between 30 and 59 mmol/L of chloride detected in a sweat test must undergo *CFTR* genetic analysis in order for a diagnosis to be made. Although many children with CF are now diagnosed at birth, individuals with non-classic CF are commonly diagnosed in adulthood.

1.3 Genetic Mechanism of Cystic Fibrosis

Homozygous or compound heterozygous pathogenic variants in the *CFTR* gene alter the quantity and/or function of CFTR protein and reduce transport of chloride, resulting in accumulation of thick dehydrated mucus. Genetic variants that cause CF are generally categorized into five variant classes (Veit et al., 2016). These variants in the *CFTR* gene cause various problems with the resulting protein including production, processing, gating, conduction, and quantity differences; these are known as classes 1, 2, 3, 4, and 5, respectively (Veit et al., 2016).

The most common pathogenic *CFTR* variant is F508del, which is a class 2 or processing variant (Veit et al., 2016). Class 1 and 2 variants result in little to no

functional CFTR protein in the cell; however, *CFTR* modulators are highly effective in restoring some functional CFTR protein for select class 2 variants, including F508del (Veit et al., 2016). Class 3 variants are known as gating defects and result in a nonfunctional CFTR protein at the cell surface. Without a *CFTR* modulator, class 3 mutations result in a classic CF phenotype; however, a robust response to a *CFTR* potentiation is seen for most class 3 variants, including G551D (Veit et al., 2016). Classes 4 and 5 result in less effective and/or less abundant CFTR channels at the cell surface (Veit et al., 2016). These variants result in reduced transmembrane conductance, but there is some residual function. As such, they are commonly referred to as “residual function” variants (Veit et al., 2016). Veit et al. (2016) reported that individuals with CF involving at least one residual function variant often have milder phenotypes including intact pancreatic function, later age at diagnosis prior to newborn screening, and lower sweat chloride than peers with two class 1-3 variants (Veit et al., 2016). Residual function variants are also highly responsive to CFTR modulator therapy. Because there are many different allele combinations, the pathogenicity of CF can vary greatly among genotypes and even among individuals with the same genotype (Veit et al., 2016).

Before the advent of modulators, CF treatment only addressed the symptoms of the disease rather than the underlying cause. Now, there are two categories of modulators (potentiators and correctors) and each works in a different way. These modulators treat the specific defect of the CFTR protein. Potentiators increase the activity of CFTR channels that are already on the

surface of cells. Correctors assist in the folding of the CFTR protein so that it is more likely to reach the surface of the cell and carry out its intended function. Because of their differing modes of action, different modulators work for different *CFTR* variants (Cuevas-Ocana et al., 2020). In 2012, the first CFTR modulator, ivacaftor, was approved in the US by the Food and Drug Administration (FDA) for qualified people with CF (Van Goor et al., 2014). Ivacaftor is a potentiator and is now approved for children older than 6 months of age with a gating mutation. Lumacaftor, a corrector, was introduced shortly after (Brewington et al., 2016). Additional correctors, tezacaftor and elexacaftor, are also available on the market and work similarly to lumacaftor. These drugs can be taken in combination in order to further facilitate CFTR protein function and thereby improve lung function as well as other morbidities associated with CF. A triple combination of elexacaftor, tezacaftor, and ivacaftor was first approved for use in the US in 2019. This drug, sold under the name Trikafta®, is now approved for use in children 6 years old and older and is applicable to the largest number of individuals with CF when compared to any other modulator (Middleton et al., 2019). For many patients, modulators have improved their quality of life and reduced many of CF's associated symptoms.

1.4 *CFTR* Expression Throughout Human Development and Spermatogenesis

The CFTR protein is expressed and specifically regulated in the apical membrane of exocrine epithelial cells of adults and children, and during key stages of fetal development. *CFTR* transcripts have been documented in the

developing pancreas, liver, kidneys, intestines, airways, epididymis, and vas deferens throughout fetal development (Tizzano et al., 1993). In contrast with the male reproductive tract, female fetuses with CF have detectable levels of CFTR mRNA in the last trimester of development (Tizzano et al., 1993). This may partially explain why fertility is more likely to remain intact for females with CF (Amaral et al., 2020).

Regarding males with CF, there are two main hypotheses as to the mechanism in which CBAVD occurs (Tizzano et al., 1993). The first is that there is a morphogenetic defect during development. Because *CFTR* expression is substantially lower in the unaffected male reproductive system than in other organs of an unaffected individual, it is thought that the development of the epididymis and vas deferens may have an increased sensitivity to *CFTR* dysfunction. However, the presence of normal ureters indicates that Wolffian ducts are functional during early development. Interestingly, typically functioning portions of the male genital tract are observed more frequently in newborns affected by CF when compared to their older counterparts. This suggests that previously normal anatomy may degenerate. The second hypothesis suggests that the male reproductive tract atrophies due to blockage caused by abnormal secretions (Tizzano et al., 1993).

Additionally, the *CFTR* gene is expressed during all stages of spermatogenesis and at its peak in round spermatids (Trezise et al., 1993). It is thought to aid in nuclear condensation and cytoplasmic volume reduction at the active transcription and transcriptional cessation stages of spermatogenesis

(Teixeira et al., 2013). The role of *CFTR* in spermatogenesis is not fully understood but is suspected to contribute to fertility status.

Typically, males with CF are counseled on fertility data that suggest only 2 to 3% of men with CF are fertile (Jarzabek et al., 2004). This data has been collected over decades of research, but very few studies have focused specifically on fertility as it relates to genotype. However, there is preliminary, unpublished data from the Medical University of South Carolina Cystic Fibrosis Center to suggest that fertility rates might be higher in men with residual function mutations when compared to men with classic *CFTR* mutations (Foil, 2021).

1.5 Fatherhood in The Context of Cystic Fibrosis

Becoming a father with CF is undoubtedly a unique experience but it is becoming increasingly more common. Limited studies have been completed that explore the experience of fathers with CF and those studies that have been completed are contradictory. One study of 22 men found that men with CF may experience rapidly declining health within 2 years of the birth of their first child (Bianco et al., 2019). This study excluded men who were on modulators or started modulators during their study and used data collected about men who fathered children from 1996 to 2018. However, a previously published study found that men with CF who are fathers did not have significantly different health statuses when compared to men with CF who were not fathers (Duguépéroux et al., 2006). Both of these studies either excluded participants who were on modulators or were completed prior to the introduction of modulators. Another study found that better or worse lung function was not significantly related to the

importance placed on having children in the future; however, men with better lung function had more difficulty coming to terms with their infertility (Fair et al., 2000).

Although there is an abundance of research about the psychosocial implications for children of parents with chronic diseases, to our knowledge there is no literature currently published about the psychosocial implications of having a parent with CF, specifically. The results of the studies that exist are also discrepant. In a systematic review of studies on children who have parents with chronic illnesses, it was reported that, although some studies have found that having a parent with a chronic illness may be beneficial in some ways, others found that the role reversal often seen in these families is harmful to a child's emotional development (Chen, 2017).

As children with CF become adults, it does not seem that their desire to have children is any less than their typical counterparts. In a survey of 94 Australian men affected by CF, 84% of them wanted to have a child (Sawyer et al., 2005). This same survey found that 17 of the 94 participants were already fathers: one by natural conception and six others via micro-epididymal sperm aspiration. The remaining ten were fathers via sperm donation or stepchildren. A study published in 2000 and completed in Scotland demonstrated that 85% of male respondents with CF felt that having a child was important to them now or would be within 10 years (Fair et al., 2000). All 22 men in Bianco et al.'s (2019) study were fathers via either natural conception or micro-epididymal sperm aspiration.

1.6 Counseling on Male Fertility and Birth Control Practices

CBAVD is the main cause of infertility in men with CF and is also the cause of infertility in 2% of infertile men in the absence of other CF features (de Souza et al., 2018). CBAVD is permanent and cannot be surgically repaired. However, some men with CBAVD can biologically father children with the help of assisted reproductive technologies, though barriers to accessing such technologies exist. In addition to obstructive azoospermia, there are other documented differences in the ejaculate of men with CF when compared to unaffected men (McBride et al., 2021; Smith, 2010). Therefore, as in all males, the presence of sperm alone is not a guarantee of fertility. In all men, sperm concentration, motility, morphology, and seminal volume are related to fertility. These factors may change over a male's lifetime. Most of these measures decrease over time; over a male's lifetime, fertility is not stagnant, and changes are likely (Harris et al., 2011). A fertility work-up that indicates intact fertility at any given time may not predict future fertility; likewise, a negative fertility work up does not indicate that a man was never fertile.

Fertility not only impacts steps that must be taken to conceive a pregnancy, but also choices that may be made to prevent undesired pregnancies. In one study of health professionals caring for adolescent males with CF, all respondents reported that they discuss infertility with their patients; however, only 38% discuss the importance of using condoms when sexually active (Sawyer et al., 2001). The effects of this may be reflected in a survey of men with CF in which 30% of respondents reported assuming they did not need

to use a condom (Sawyer et al., 2005). Rates of condom usage are known to vary by demographic factors and relationship status and may be lower in the CF population than the general population based on the assumption of infertility (Reece et al., 2010).

1.7 Male Outlook on Infertility

The majority of studies on infertility outlook focus on women, both in the general population and in cases of CF. However, studies have shown that infertility is no less distressing for men than it is for women (Fisher and Hammarberg, 2012). In fact, Fair et al. (2000) discovered that men with CF are more likely to desire a child than women with CF; 85% of men felt having a child in the future was important compared to 72% of women (Fair et al., 2000). In couples affected by infertility, both partners were more likely to experience negative emotions and heightened anxiety. However, these studies were all completed after a person learned of infertility, generally due to the inability to conceive a child. Few studies have been done to evaluate the outlook and attitude of men with probable infertility prior to attempts at conception, though some specifically focusing on men with CF exist (Fair et al., 2000; Sawyer et al., 2005).

A study of 94 Australian men with CF found that 50% of participants were upset when they learned about fertility problems (Sawyer et al., 2005). In the same study, 42% of participants reported that infertility had become a greater problem over time and 22% felt that infertility had affected their personal relationships. Sawyer et al. (2005) reported that the timing and educator also

affected a patient's initial reaction to information about infertility. Men who learned of infertility from an information source other than the one they indicated as their preference had a more negative reaction to the information. Of note, men reported several different preferred sources of education, and this is likely based on the individual person (Sawyer et al., 2005).

A study of 116 Scottish men with CF also examined male education on infertility in males (Fair et al., 2000). Only men were presented with survey questions specifically about male fertility counseling. The men in this study reported various ages and sources of education when asked how they learned about infertility. Importantly, when asked how they felt when they learned about infertility, respondents most commonly indicated that they felt "shocked" (40%), "bewildered" (24%), and "angry" (19%) (Fair et al., 2000). Only 24% of men reported feeling "not bothered" when they learned of infertility, regardless of age or education source (Fair et al., 2000). Overall, Fair et al. (2000) concluded that fertility counseling should begin in early adolescence and felt that it was the responsibility of the CF center to offer information about infertility to their patients.

Although both of the above publications offer important background on the outlook of fertility in men with CF, they were both completed prior to the advent of modulator therapy and outside of the US (Fair et al., 2000; Sawyer et al., 2005). It is reasonable to hypothesize that improvements in quality of life and increase in life expectancy due to modulator therapy may increase the desire to have children and therefore lead to a negative reaction to probable infertility. Additionally, sex education for adolescents varies around the world (Lameiras-

Fernándex et al., 2021). These differences may influence attitudes of the studied population and necessitate a closer look at a US focused population.

1.8 Spermcheck® Fertility Home Test for Men

The SpermCheck® Fertility Home Test for Men (SCFT) was approved for home use by the FDA in 2010 (Chan, 2010). The SCFT is a rapid qualitative immunodiagnostic home test that detects the presence of sperm in semen. Sperm are detected using antibodies against sperm acrosome-specific protein analyte SP10. This test underwent validation through a study that found it to be 96% accurate at detecting normal sperm count (greater than or equal to 20,000,000 sperm/mL), oligozoospermia (between 5,000,000 and 20,000,000 sperm/mL), and severe oligozoospermia (less than 5,000,000 sperm/mL) when used correctly (Chan, 2010). The originally marketed test consisted of two immunochromatic strips in a single cassette and is intended to be read visually. One strip gave a positive result if sperm concentration is 20,000,000 sperm/mL or greater (normal), and the other strip gave a positive result at 5,000,000 sperm/mL and above (oligospermia). The presence of no test lines on the cassette after proper use indicated severe oligozoospermia (less than 5,000,000 sperm/mL) or azoospermia (no sperm present in the ejaculate). Because CBAVD results in azoospermia, this test was expected to perform particularly well in detecting the type of infertility most common in CF. The SCFT is now sold as a single cassette that includes only one immunochromatic strip. This functions identically to the strip on the original test that detected sperm at a 20,000,000 sperm/mL concentration. Meaning, the currently marketed SCFT can only detect

normal sperm count and lower than expected sperm count; not distinguishing between oligospermia and azoospermia.

1.9 Rationale

CF continues to be among the most common serious autosomal recessive conditions. The birth incidence of CF has been recently reported as 1 in 4,000 in the US population, though incidence varies significantly among ethnic groups and is highest in those of Northern European descent (Scotet et al., 2020). Further, improved CF testing, including newborn screening and *CFTR* gene sequencing, have enabled clinical recognition of a broader phenotypic range of CF and CFTR-related disorders, where milder cases, often involving residual function variants, may have been missed in the past (Scotet et al., 2020). With the advent of highly effective modulator therapy and other treatment advances, more than half of people with CF are now adults and routinely reach ages that they may become sexually active and consider starting a family (CFF, 2021; Hull & Kass, 2000). Increase in lifespan and improved quality of life emphasize the need for fertility counseling and work-up to become accessible for all interested individuals. This information will enable informed decision making about sexual and reproductive health.

Further investigation into the experiences of men with CF is needed in order to optimize fertility counseling and create specific suggestions for how adolescents may be educated regarding fertility. This study provided an updated and more culturally focused evaluation of the perspectives and outlooks on fertility of men with CF in the context of their previous education on fertility.

Identifying common feelings and beliefs held by men with CF about birth control and potential fatherhood may help healthcare providers deliver more focused counseling pertaining to concerns about fertility. This may improve overall quality of life for these individuals and families, as well as benefit the CF community as a whole.

There is also a need for more research on experiences with clinical fertility testing, specifically for men with CF who are interested in learning their fertility status. It is our hope to further illustrate the need for fertility testing in all men with CF who are interested in learning their fertility status. Personalized fertility information can not only influence logistical choices when it comes to planning for the future, but may also resolve feelings of uncertainty about fertility for men with CF. In the current study, information regarding how men feel about their fertility status when they have individualized information was gathered. Gaining insight on possible changes in each participant's perspective on fertility and family planning, especially if they receive results that confirm their previously assumed fertility status, will contribute to the CF community by adding to the body of evidence that supports providing more options for fertility testing. Because of the diversity in mutation status and combinations of mutations, data gathered on some men with CF may not be useful for all men with CF. This study could also provide methodology to support more extensive future research into fertility rates among men with CF, including those with residual function variants, specifically.

1.10 Purpose

The current study aimed to evaluate perceptions of fertility, outlook on future children, and birth control practices in men with CF. Perceptions of fertility may influence sexual health practices, relationships, and family planning of adult men with CF who have been previously counseled about infertility in males with CF. Previous studies have closely evaluated attitudes of men with CF surrounding fertility, fatherhood, and condom usage (Fair et al., 2000; Sawyer et al., 2005). However, with profound developments in treatment, a change in these attitudes is possible. Additionally, family planning and fertility outlook both have large cultural influences that may be unique in specific countries; both of the above studies were completed outside of the US. The current study utilized an online survey, distributed through Facebook groups, in order to evaluate the previous counseling that men with CF received regarding fertility and their subsequent perception and outlook on family planning. Demographic information, CF history, previous education on infertility, current number of children, and desire for a child in the future were evaluated. Perceptions of fertility status, feelings of anxiety and embarrassment, as well as birth control practices were also analyzed.

Additionally, a second part of the study evaluated participant experience using a SCFT and compared fertility outlook before and after receiving results from the SCFT. This FDA approved at-home semen analysis kit provided them with information about sperm count in the privacy of their own home. A short phone interview after reading their results was conducted to collect information

about their results and evaluate if these results change their perceptions of their fertility. Additionally, ease of use of at-home semen analysis was examined in this select group of participants in order to assess the feasibility and patient perceptions of home fertility testing for men with CF.

1.11 Study Design

The current study utilized a mixed-methods approach to examine current perceptions and outlook on fertility, family planning, and birth control use in men with CF. An online survey was distributed through various Facebook groups. This survey collected information regarding demographics, CF history, previous fertility education, number of current children, desire for future children, and outlook on fertility and birth control use. At the conclusion of the survey, participants were invited to participate in part two of the study. In part two of the study, participants were provided with a SCFT to complete, and a phone interview followed. The phone interview was used to determine potential fertility in the participants, to evaluate any possible changes in fertility outlook based on their results, and ease of use of the SCFT for this study population.

CHAPTER 2

INFERTILITY EDUCATION FOR MEN WITH CYSTIC FIBROSIS AND ITS EFFECTS: OUTLOOKS ON FERTILITY AND BIRTH CONTROL[1]

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2.1 Abstract

Many men with Cystic Fibrosis (CF) are infertile; however, few studies have evaluated fertility outlook of men with CF since the advent of modulator therapy. As predicted survival and quality of life improve, family planning is an area of increased interest for the CF community. The current study surveyed men with CF to explore their outlook on fertility, family planning, and birth control use with the option to receive a home fertility test and follow-up interview with study staff.

Seventy-five men with CF completed the survey and 53 (71%) believed they were likely infertile. Most recalled learning about infertility between age 10-20 years and from a healthcare provider. Forty participants (53%) reported a previous clinical sperm count, with 27 (68%) reporting infertility. Four participants completed at-home fertility tests, all of which were negative. These participants found home testing valuable and easy to complete.

Seventeen participants (23%) indicated they had a child through various means: biological, donor conceived, adopted, or stepchild. Most participants (65%) indicated they wanted a child in the future. Men who have taken modulators were significantly more likely to desire a child in the future than those who have not (77% versus 53%), and to feel that they would enjoy parenting a child (87% versus 67%).

Using condoms for pregnancy and/or sexually transmitted infection prevention at any time was reported by most heterosexual participants (52/70,

74%). However, some participants (39/70, 56%) reported not feeling obligated to use birth control due to the likelihood of infertility.

Rates of known or assumed CF related male infertility are lower in this cohort than expected. Our findings highlight opportunities for improved fertility education including family building options, safe sex practices, and access to semen analysis. Preliminary data support potential utility of home semen analysis, which should be explored further in future research.

2.2 Introduction

With a birth incidence reported to be 1 in 4,000, Cystic Fibrosis (CF) remains one of the most diagnosed recessive genetic disorders in the United States, although incidence varies significantly among ethnic groups (Scotet et al., 2020). CF is a complex, multisystem disease that affects the respiratory, digestive, reproductive, and other systems caused by the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (Kerem et al., 1989). Many more individuals with CF are living into their adult years, with a median predicted survival of 59 years in 2020 (CFF, 2021). This is a striking improvement over previous decades and represents significant improvements in medical interventions and support developed for people with CF.

As the medical world has developed more effective methods of treating the most significant morbidities associated with CF, as well as treatments to address the underlying genetic causes of CF, people with CF are able to achieve numerous lifetime goals. For men with CF who desire to become a father, accomplishing this goal may be complicated, as many men with CF experience

infertility (McBride et al., 2021). Although men with CF produce sperm, many are born with a condition known as congenital bilateral absence of the vas deferens (CBAVD) (Barreto et al., 1991). This is the main cause of infertility in men with CF and cannot be surgically repaired (de Souza et al., 2018). CBAVD is a form of obstructive azoospermia. Typically, CBAVD cannot be accurately diagnosed using a physical exam and is generally diagnosed using ultrasound (Lin & Huang, 2020).

Without the vas deferens, natural conception is impossible. However, with advances in reproductive technology, sperm retrieval and intracellular insemination is now possible and allows men with CBAVD to become biological fathers (McBride et al., 2021). Additionally, alternative family building options, such as adoption and sperm donation, may allow some males with CF to experience fatherhood. Despite all of these options, barriers may exist between men with CF and access to optimal fertility counseling and testing.

The majority of studies on infertility outlook focus on women, both in the general population and in cases of CF. However, studies have shown that infertility is no less distressing for men than it is for women (Fisher and Hammarberg, 2012). In fact, Fair et al. (2000) discovered that men with CF are more likely to desire a child than women with CF; 85% of men felt having a child in the future was important compared to 72% of women. In a survey of 94 Australian men affected by CF, 84% of them wanted to have a child (Sawyer et al., 2005). This same survey found that 17 of the 94 participants were already fathers: one by natural conception and six others via micro-epididymal sperm

aspiration. The remaining ten were fathers via sperm donation or stepchildren. Although few studies have been done to evaluate the outlook and attitude of men with known probable infertility prior to attempts at conception, some specifically focusing on men with CF exists (Fair et al., 2000; Sawyer et al., 2005).

Sawyer et al. (2005) found that 50% of participants were upset when they learned about fertility problems. In the same study, 22% of participants felt that infertility had affected their personal relationships. Sawyer et al. (2005) reported that the timing and educator also affected a patient's initial reaction to information about infertility. Men who learned of infertility from an information source other than the one they indicated as their preference had a more negative reaction to the information. Of note, men reported several different preferred sources of education (i.e., medical professional and family), and this is likely based on the individual person (Sawyer et al., 2005).

A study of 116 Scottish men with CF also examined male education on infertility (Fair et al., 2000). Men were presented with survey questions specifically about male fertility counseling. The men in this study reported various ages and sources of education when asked how they learned about infertility. Importantly, when asked how they felt when they learned about infertility, respondents most indicated that they felt "shocked" (40%), "bewildered" (24%), and "angry" (19%) (Fair et al., 2000). Only 24% of men reported feeling "not bothered" when they learned of infertility, regardless of age or education source (Fair et al., 2000). Overall, Fair et al. (2000) concluded that fertility counseling

should begin in early adolescence and felt that it was the responsibility of the CF center to offer information about infertility to their patients.

Fertility not only impacts steps that must be taken to conceive a pregnancy, but also choices that may be made to prevent undesired pregnancies. In one study of health professionals caring for adolescent males with CF, all respondents reported that they discuss infertility with their patients; however, only 38% discuss the importance of using condoms when sexually active (Sawyer et al., 2001). The effects of this may be reflected in a survey of men with CF in which 30% of respondents reported assuming they did not need to use a condom (Sawyer et al., 2005).

Although the above publications offer important background on the outlook of fertility in men with CF, they were completed prior to the advent of modulator therapy and those that surveyed patients took place outside of the US (Fair et al., 2000; Sawyer et al., 2001; Sawyer et al., 2005). For many patients, modulators have improved their quality of life and reduced many of CF's associated symptoms. Additionally, sex education for adolescents varies around the world (Lameiras-Fernández et al., 2021). These differences may influence attitudes of the studied population and necessitates a closer look at a US focused population.

Our research aimed to understand the outlook on fertility, family planning, birth control, and contributing factors for men with CF. It is reasonable to hypothesize that improvements in quality of life and increase in life expectancy due to modulator therapy may increase the desire to have children and therefore

a negative reaction to probable infertility. Exploring this hypothesis was a main goal of the current study. The current study also piloted a possible method for providing men with CF personalized fertility information using the SpermCheck® Fertility Home Test for Men (SCFT). The SCFT was approved for home use by the Food and Drug Administration (FDA) in 2010 and can be used by men to screen for potential fertility (Chan, 2010). The current study assessed a limited number of participants' perspective of the ease of use with this at-home test and determined if the results may have affected their perspective of their own fertility.

2.3 Methods and Materials

2.3.1 Participants and Recruitment

Participants were invited to take part in an online survey (Appendix A) via a flyer (Appendix B) distributed by Cystic Fibrosis Centers and social media groups. Social media posts included a digital copy of the flyer circulated to the following Facebook pages and groups: Cystic Fibrosis, Cystic Fibrosis Foundation, Cystic Fibrosis Community, and Trikafta/Kaftrio Cystic Fibrosis. Inclusion criteria, goals of the study, researcher contact information, and a QR code for direct survey access were included on the flyer. In order to take part in this study, participants had to be over the age of 18, assigned male at birth, have a diagnosis of CF, and be fluent in English reading and writing. Taking the survey was voluntary; participants could exit the survey at any time. Upon completion of all survey questions, participants were presented with a link to an additional questionnaire (Appendix C) where they could register to receive a $5 Amazon e-gift card, if they were one of the first 50 participants.

At the end of the survey, participants had the opportunity to indicate if they were interested in the second part of the study (part two) which included receiving and completing the SCFT as well as a follow up phone interview to discuss their results. If interest in part two was indicated, the primary investigator called the participant using the provided phone number to explain the process that would be involved in part two. A script was used to ensure all points were covered (Appendix D). This included explaining the possible benefits and risks as well as answering any questions. If the participant was still interested, they provided an email address to which a consent form (Appendix E) was sent. All consent processes, survey materials, and the study as a whole was approved by the University of South Carolina Institutional Review Board (ID: Pro00117594).

2.3.2 Procedure

The online survey was created through Qualtrics.com and included multiple choice, open-text, and Likert scale items. Survey items inquired about participant demographics, CF history, number of current children, number of children desired, outlook on fertility, and outlook on family planning. All questions were voluntary, excluding questions required to determine if participants met inclusion criteria. The survey was open from January 6, 2022, to February 4, 2022. A total of 300 responses to the survey were recorded. Only 277 of these met the inclusion criteria for the study. However, a number of these responses were found to be fraudulent; therefore, a method for eliminating the fraudulent responses from the data set was designed (Figure 2.1). A combination of recommendations from various sources was used to develop this data sieve

(Qualtrics, 2021; Simone, 2019). Ultimately, 75 responses were included in data analysis.

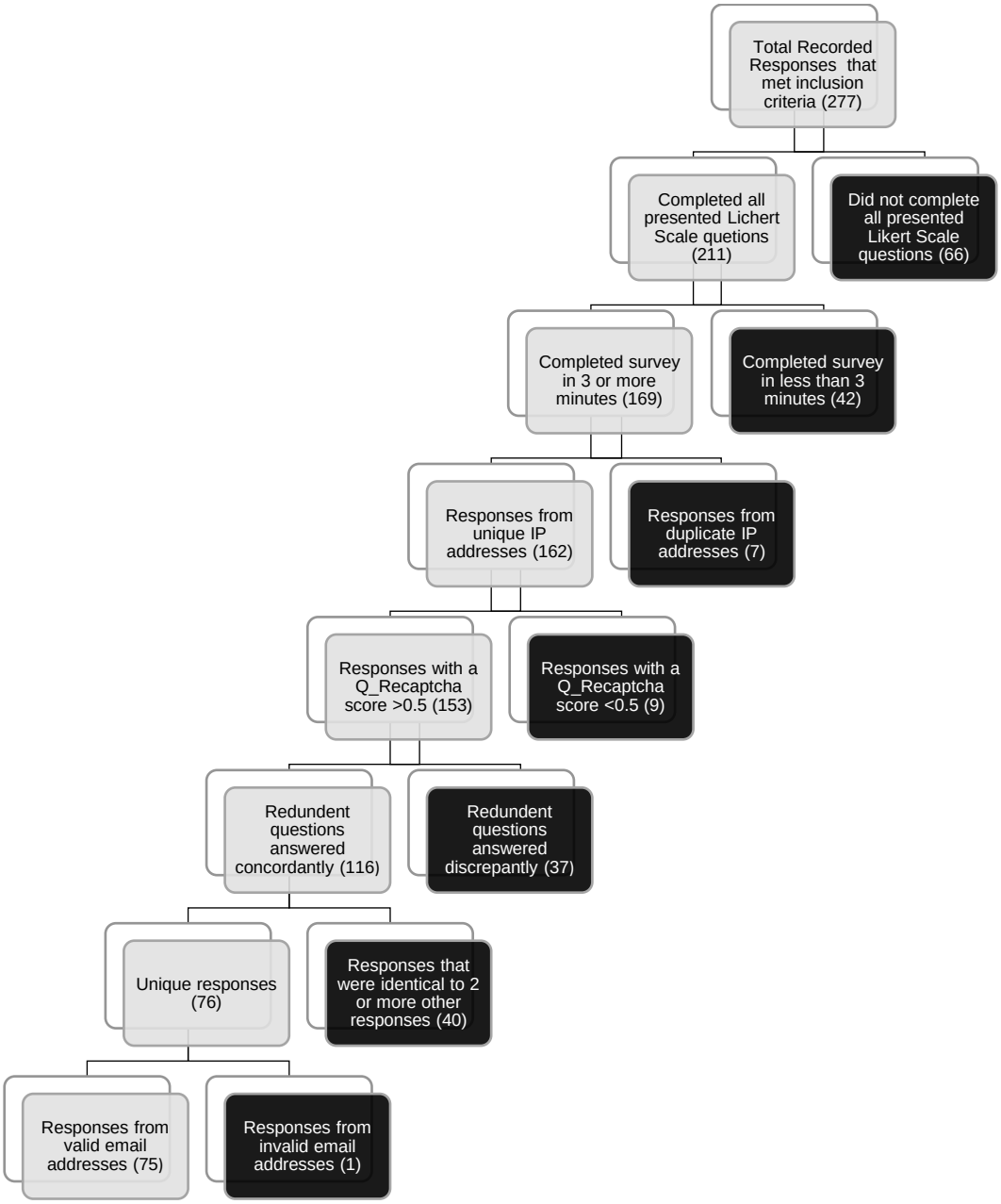

Figure 2.1 Methods by which survey responses were filtered to maintain data integrity. Responses included in black boxes were excluded from the data analysis.

Thirteen survey respondents indicated that they would like to learn more about part two of the study. These respondents were contacted by the primary

investigator using the information provided in the last questions on the survey. This initial phone call followed a script (Appendix D) to ensure that all relevant information was disclosed. At the conclusion of this phone call, participants were asked to provide an email address if they were still interested in participating in part two of the study. Nine participants provided an email address in order to receive the written consent form (Appendix E). Four participants returned a signed consent form via email. These four participants were called to schedule a time for a phone interview and obtain needed information for shipping the SCFT. This phone call followed a script to ensure relevant information was disclosed (Appendix F).

After the phone interview was scheduled and the SCFT was sent, an email (Appendix G) including SCFT instructions (Appendix H) was sent to the participant. The SCFT is a rapid qualitative immunodiagnostic home test that detects the presence of sperm in semen. An immunochromatic strip functions to detect sperm at a 20,000,000 sperm/mL concentration. Meaning, the SCFT can detect normal sperm count and lower than expected sperm count; not distinguishing between oligospermia and azoospermia. SpermCheck® also produces an at-home post-vasectomy sperm test that can detect the presence of sperm at a concentration of 250,000 sperm/mL. All four participants were then called at the scheduled time and semi-structured interviews were conducted (Appendix I). These interviews were recorded via audio recording and then transcribed by hand. Recordings were destroyed after transcription.

2.3.3 Data Analysis

Quantitative survey data was analyzed using descriptive statistics and assessed for correlations utilizing Microsoft Excel and IBM Statistical Package for the Social Sciences (SPSS) version 28.0.0.0 (190). In order to improve data analysis, the five-point Likert scale questions were combined into three-point scales. Strongly agree and agree were combined into agreement; strongly disagree and disagree were combined into disagreement. This increased group sizes for agreement and disagreement while maintaining authentic data. A chi-square test of goodness-of-fit was performed via SPSS to determine if there was a significant relationship between desire for a future child and whether participants had taken modulator therapy. A similar test was also performed to determine if there was a significant relationship between the participant feeling they would enjoy parenting a child and whether they had taken modulator therapy. An alpha level of .05 was used for all statistical tests.

Some open response questions were also combined into categories including the number of current and desired children, as well as the educator who explained the likelihood of infertility in men with CF. For questions that were not answered that required numbers, zeros replaced missing data. For unanswered questions that required descriptive responses, “no response” was recorded.

Interview responses were analyzed for themes, but due to small sample size, these responses were ultimately summarized, and quotes were used to support concepts evaluated in the survey. There were several close-ended, yes

or no questions in the phone interview; these responses are reported in frequencies.

2.4 Results

2.4.1 Demographics

The age of participants ranged from 18-60 years old; the average age of participants was 31 years old. The majority of participants were 30 years old or younger, white or Caucasian, and non-Hispanic (Table 2.1). The respondents reported mostly being sexually attracted to women, exclusively (92%), while a few were sexually attracted to only men (7%) or attracted to women, men, and non-binary people (1%). Most participants were single (41%), 27% were in long-term relationships, and 32% were married.

Table 2.1 Participant Demographics

Participant demographics (N=75)		Total (n)	Percentage (%)
Age			
	18 to 30 years old	45	60%
	31 to 40 years old	19	25%
	41 to 50 years old	6	8%
	51 to 60 years old	5	7%
Race			
	White or Caucasian	55	73%
	Black or African American	16	21%
	Other	2	3%
	Native Hawaiian or other Pacific Islander	1	1%
	No response	1	1%
Ethnicity			
	Non-Hispanic	60	80%
	Hispanic or Latino	3	4%
	No response	12	16%

2.4.2 Cystic Fibrosis History

Participants reported a variety of genotypes (Figure 2.2). As expected, F508del (n=44) was the most commonly reported variant followed by R117H (n=12), G542X (n=10), and G551D (n=7). Seven participants did not know their genotype and 38 participants only reported one variant. Of the total 75 participants, 54 (72%) indicated that they were pancreatic insufficient and 39 participants (52%) indicated that they have taken or are currently taking modulators.

Class 1	Class 2	Class 3	Class 4	Class 5
• G542X • R553X • 621+1G>T • Q685X • W1282X • E585X • 1717-1G • 2184delA	• F508del • N1303K • I507del	• G551D	• R117H • D1152H	• 2789+5G-A

Figure 2.2 Reported *CFTR* variants by class

Age ranges were used to elicit how old participants were at the time of diagnosis. Almost half of participants (48%) were diagnosed at less than 1 year of age, 23% of participants were diagnosed with CF between the ages of 1 and 9 years old, 12% were diagnosed between 10 and 19 years old, 15% were diagnosed with CF at 20 years old or older, and 2% of participants did not report their age at diagnosis.

2.4.3 Fertility Data

Four of the 75 participants (5%) reported they did not recall any previous education about the possible infertility for men with CF. Participants who indicated they had learned about possible infertility for men with CF were asked to recall their age when they learned about infertility and who took on the role of educator (Table 2.2). Participant responses regarding who educated them about the possibility of infertility were categorized into the following groups: medical professionals, family, self-educated, or other. The two responses that fell into the other category reported being told by “other CF patients and their parents” and “a random classmate”.

Table 2.2 Recollection of Infertility Education Timing and Source

Education on Infertility (N=75)	Total (n)	Percentage (%)
At what age did you learn about possible infertility?		
Less than 10 years old	4	5%
Between 10 and 15 years old	22	30%
Between 16 and 20 years old	30	40%
21 years old and older	15	20%
Never	4	5%
Who taught you about possible infertility?		
Medical Professional	35	49%
Self-Educated	13	18%
Family	7	10%
Other	2	3%
No response	14	20%

The four respondents who did not recall any education about CF related infertility from any source were spread among various ages of diagnosis; however, all men who reported being diagnosed under the age of one year old did recall being educated about infertility (Table 2.3).

Table 2.3 Recollection of Infertility Education by Age at Diagnosis

Age at Diagnosis (N=75)	Recall Education n (%)	Do Not Recall Education n (%)
Less than 1 Year Old	36 (100%)	0 (0%)
Between 1 and 9 Years Old	16 (94%)	1 (6%)
Between 10 and 19 Years old	7 (78%)	2 (22%)
20 Years Old or Older	10 (91%)	1 (9%)

Most respondents recalled being educated about infertility between the ages of 10 and 20 years old (Figure 2.3). Medical professionals were the most reported source of information in all age groups, with the exception of males who were under the age of 10 when they first learned of infertility in men with CF.

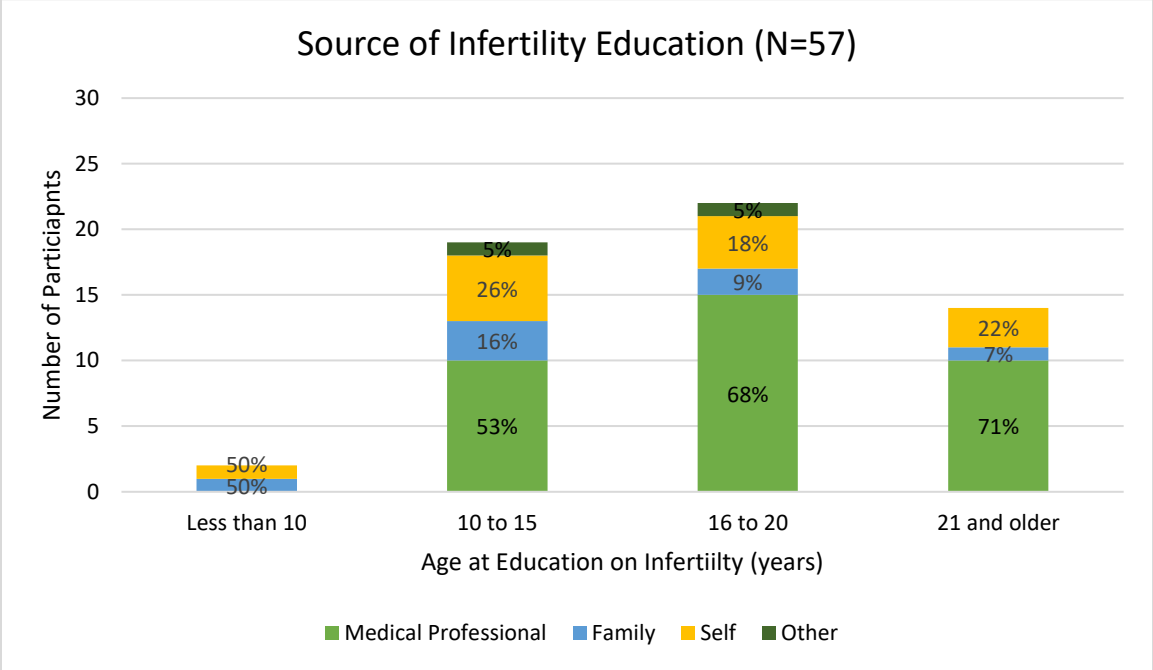

Figure 2.3 The age at which participants were educated about possible infertility and their source of education

A previous clinical sperm count was reported by 40 participants (53%). Age at which semen analysis took place was not collected; however, current age was considered. Only one participant currently under the age of 20 reported having completed a clinical sperm count. Further, only 18 out of 45 participants

who were 30 years old or younger had completed a clinical sperm count. Of the 40 participants who had completed a sperm count, five participants (13%) indicated a typical number of sperm. Of these five men, two of them reported having biological children. Two had at least one F508del variant, one reported his genotype as R1177H and G542X, and the remaining two reported only one variant- G542X and R117H, respectively.

Of the four men who completed the SCFT, all men had results that indicated a sperm count less than 20,000,000 sperm/mL. All of these men reported at least one F508del variant in *CFTR*.

2.4.4 Number of Children

Most participants (n=58, 77%) did not have any children at the time of the survey. However, some participants (n=17, 23%) reported that they did have children via various family building methods- biologically, via donor sperm, adoption, or stepchildren (Table 2.4). Mode of conception for biological children was not elicited. Although participants had the opportunity to report children whom they were unsure if they were the biological child, no participants reported any children of uncertain paternity.

Table 2.4 Current Number of Children

Number of Current Children (N=75)	Total (n)	Percentage (%)
Biological		
Zero	65	87%
One or more	10	13%
Donor		
Zero	74	99%
One or more	1	1%
Adopted		
Zero	72	96%
One or more	3	4%

Step			
	Zero	71	96%
	One or more	4	6%

Using Likert scales, 58 participants (77%) agreed that they would enjoy some or all aspects of being a parent and 49 participants (65%) indicated that they would like to have at least one additional child in the future through various means. Of the 20 participants who were in long-term relationships, 18 (90%) desired a child in the future, the most likely among all relationship statuses reported. Of participants who were married, 14 out of 24 desired a child in the future (58%).

Single participants were the least likely, although not unlikely, to report that they desire a child in the future with 17 out of the total 31 single participants indicating they would like a child in the future (55%). Single men under the age of 30 reported wanting a child or not wanting a child in the future at equal rates. Those in the age groups most likely to want a child in the future, 18 to 30 years old and 31 to 40 years old, were also most likely to be in long-term relationships or married.

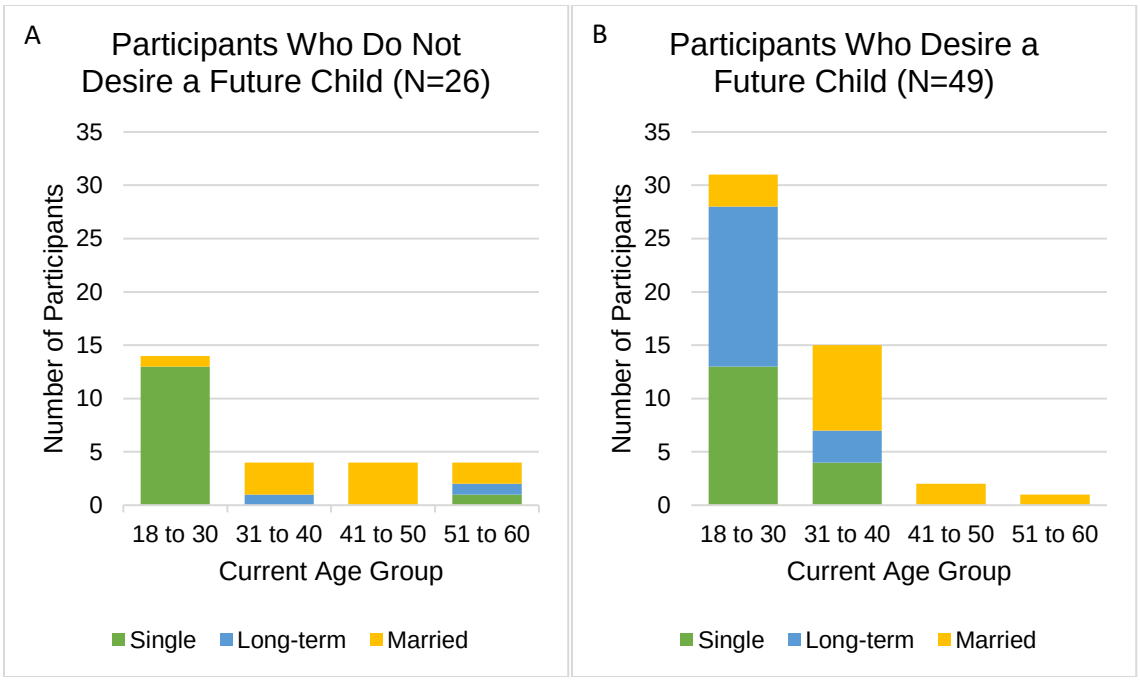

Figure 2.4 Relationship status of participants who do and do not desire a future child.

Participants' desire for a future child was also considered in the context of whether they had taken modulator therapy (Figure 2.5). A chi-square test of goodness-of-fit was performed to determine if desire for a future child was equally distributed among the two groups. A significant relationship was found, X^2 (1, N=75) =4.82, p=.028. Out of our 75 participants, 39 indicated they were taking or had taken modulators in the past. The remaining 36 had not taken modulators. Those who had taken modulators were more likely to indicate that they desire a child in the future. Participants who had taken modulators were also significantly more likely to report that they felt they would enjoy parenting a child, X^2 (2, N=75) =6.07, p=.048.

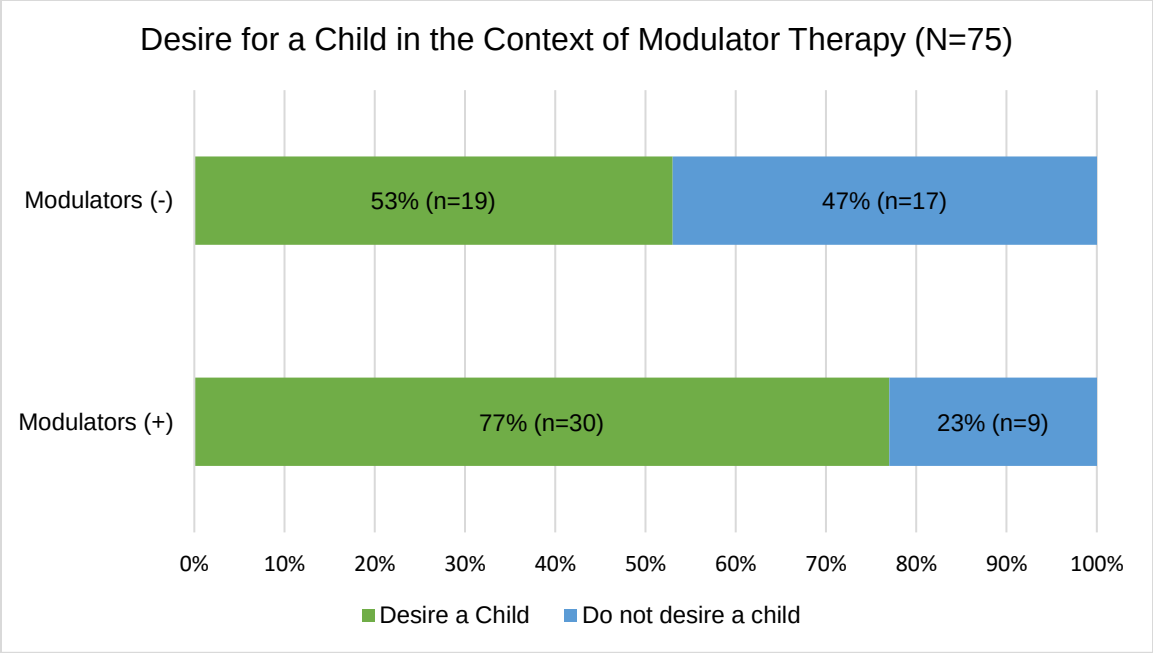

Figure 2.5 Desire for a child in the context of modulator therapy status

Out of 75 total participants, 60 (80%) agreed that they have wanted a biological child at any point. Of those 60 participants, 41 indicated that they currently desire a biological child in the future (68%). Additionally, 5% of participants indicated that they would like to have a child via sperm donation, 11% indicated that they would like to adopt a child, and 5% indicated they would like to become a father figure to stepchildren in the future.

2.4.5 Outlook on Fertility

Likert scale items regarding outlook on fertility were categorized into three categories: perception, anxiety, and embarrassment (Table 2.5). Responses were described by the source of fertility information (Figure 2.6), age at education, and current age. No statistical difference was appreciated when comparing perception questions by source of education, age at education, or current age. Most participants felt they were likely infertile and agreed that their

perception of their fertility had affected their family planning. All 75 participants responded to each of these statements.

Table 2.5 Outlook on Fertility

Outlook on Fertility (N=75)	Agree n (%)	Neutral n (%)	Disagree n (%)
Perceptions			
I feel that I am likely infertile	53 (71%)	13 (17%)	9 (12%)
I feel that my perception of my fertility has affected my family planning	39 (52%)	21 (30%)	15 (20%)
I think infertility is a significant burden of Cystic Fibrosis	51 (68%)	17 (23%)	7 (9%)
Anxiety			
I have felt worried that I would not be able to father a biological child	43 (57%)	22 (30%)	10 (13%)
I have felt worried about how my fertility may affect my romantic relationships	42 (56%)	13 (17%)	20 (27%)
Embarrassment			
I have felt embarrassed about the possibility that I may be infertile	35 (47%)	15 (20%)	25 (33%)
I have avoided disclosing information about my fertility to romantic partners in the past	29 (39%)	15 (20%)	31 (41%)

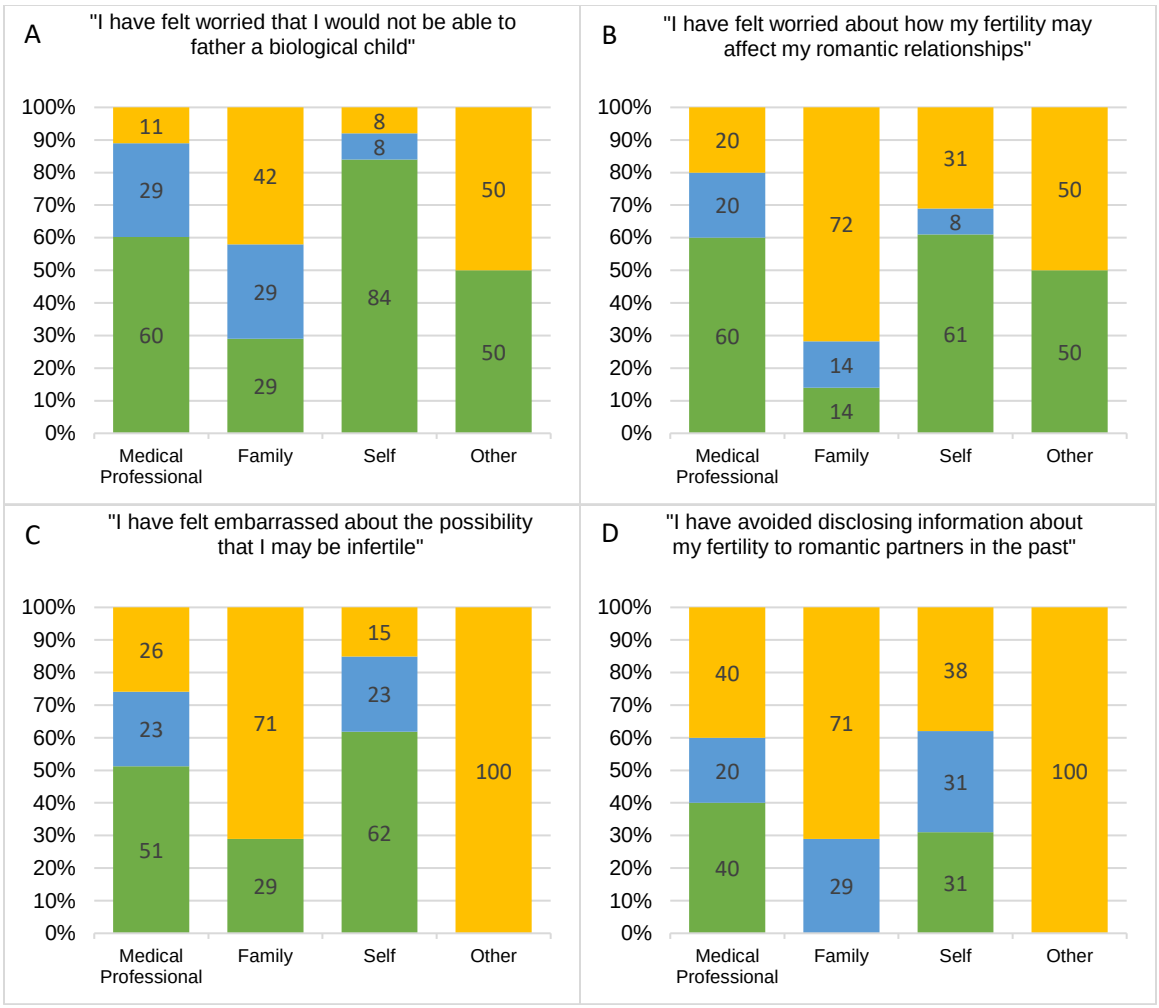

Figure 2.6 Frequency of agreement (green), neutrality (blue), and disagreement (yellow) with statements used to evaluate fertility outlook by information source: Medical Professional (n=35), Family (n=7), Self (n=13), and Other (n=2)

2.4.6 Birth Control Practices

Using Likert scales, participants who responded that they were sexually attracted to women (n=70) indicated if they agreed or disagreed with specific statements regarding personal use of birth control (Table 2.6). Participants also had the option to indicate that their feelings were neutral about any of the presented statements. These statements were used to assess each individual's outlook on birth control and condoms.

Table 2.6 Outlook on Birth Control

Outlook on Birth Control (N=70)	Agree n (%)	Neutral n (%)	Disagree n (%)
Perceptions			
My knowledge or perceptions of infertility have changed my personal use of birth control methods, including condoms, in the past	46 (66%)	12 (17%)	12 (17%)
Responsibility			
I do not feel obligated to use birth control or condoms for the purpose of preventing pregnancy because of my assumed fertility status	39 (56%)	17 (24%)	14 (20%)
I rely on my partner to take responsibility to prevent pregnancy	17 (24%)	18 (26%)	35 (50%)

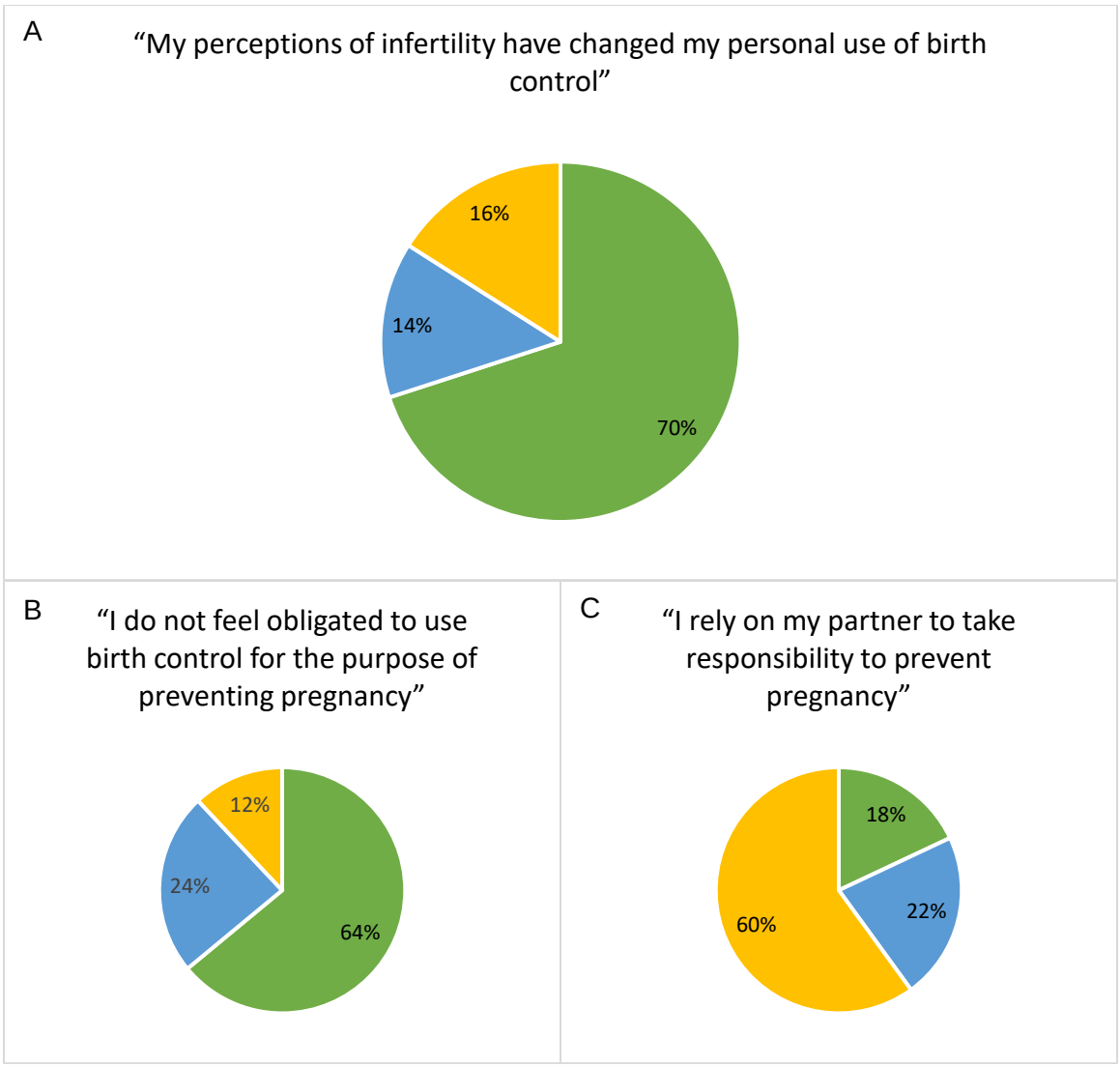

Figure 2.7 Frequency of agreement (green), neutrality (blue), and disagreement (yellow) for men who are attracted to women and feel they are likely infertile with statements used to evaluate outlook on birth control (n=50)

Of respondents who felt that they were likely infertile, 70% agreed that this altered their use of birth control in the past (Figure 2.7 A). Only 31% of respondents indicated that their perception of their fertility changed both their plans to have children and their plans to avoid having children and 4% indicated that their understanding of their fertility changed neither their plans to have children or prevent pregnancy.

The level of how responsible respondents felt to prevent a pregnancy was also evaluated. Nearly equal numbers of men who feel they are likely infertile do not feel obligated to use birth control to prevent pregnancy (Figure 2.7 B) and do not rely on their partner to prevent pregnancy (Figure 2.7 C).

When asked about condom use, 69% of respondents reported having used a condom in the past for any reason. Men who were educated about infertility by family members were the most likely to report that they have used condoms in the past for any reason (86%). Those who learned about infertility independently reported the lowest use of condoms (50%).

2.4.7 Phone Interviews

Of the four participants who completed the SCFT, all of them completed the test, had results that indicated a below typical sperm count, felt that the instructions that came with the test were easy to follow, understood how to read the results of the test, believed the results of the test were accurate, and felt that access to this type of test would be helpful to other men in the CF community. None of the respondents felt that the results of the test would change their current birth control practices or family plans. Quotes from the respondents were organized by themes (Table 2.7). One of the themes, relief from confirming assumed infertility was cited by interviewees as the biggest reason they felt access to this test would help others.

Table 2.7 Themes Identified in Phone Interviews

Themes Identified in Phone Interviews (N=4)
Initial sadness
"I kind of expected the results that I got, but at the same time it was… …eye opening? … I don't know. It made me feel sad for a few seconds. Like the realization of it, but… …I expected it."
Sense of relief from confirmation of assumed infertility
"I think it's just a way of probably confirm[ing] things. Because, you know, within clinic and stuff they talk about it but there's no real way of testing or anything. They don't give you any options as far as how to test certain things."
*"It's nice to officially know. *laughs* So I guess there's less of the doubt in my head. Like 'well, you know, I technically don't know' so now I believe it. I was kind of expecting it. I was 99.9% sure this would be the case. So, it's nice to have that confirmation."*
"Like 90 plus, probably even north of 90 plus, you know, do not have the vas deferens. So that's always just what is taken for gospel but, you know, I'm happy that we are kind of able to confirm it in our own right versus just being told something and believing it."
"I guess it'd give you an idea and kind of answer, maybe sum up or answer some questions you might have about yourself fertility wise."
"I had a pretty good idea I wasn't fertile, but it's good to have information on stuff. Be able to pass information along."

Lack of resources or options for fertility information and testing
“I wish I knew more about how available it was. For what it’s worth I thought I always had to go to like a LabCorp or like a professional diagnostic agency to get this done, not at home.”
“Had I known this was so affordable and I could do it from the comfort of my own home I honestly probably would have done it back in my early 20s.”
“[Infertility is] something that the patient is going to deal with forever. They should at least know everything can know about it.”
“I mean you get information on everything else. They have booklets and packets for everything else, but they don’t have hardly anything on that.”

2.5 Discussion

2.5.1 Infertility Education

Most men in this study were diagnosed with CF early in life and recalled learning about possible CF related infertility at some point. However, some participants reported being diagnosed with CF later in life after being diagnosed with infertility. Few participants reported that they had not been previously educated about the possible infertility for men with CF, which aligns with studies by Sawyer et al. in 2005 and Fair et al. in 2000 who each found similar rates of men who did not recall infertility education. However, it is possible that many of these men or their primary caretakers may have been educated about infertility, but men did not remember that conversation at the time of the survey. Record review was not possible in the current study to assess if men truly did receive

infertility education. A publication, which surveyed medical professionals who care for men with CF in Massachusetts, found that all participants reported they speak to adolescent patients about probable infertility (Sawyer et al., 2001). If that is consistent across all healthcare providers, there may have been some form of infertility education that was not recalled by our participants.

Sawyer et al. (2005) found that males were most likely to be educated about possible infertility between the age of 16 and 20 years, with the average age at education being 16 years old. The majority of our participants also recalled being educated in the same age range. On average, Sawyer et al. (2005) found their participants preferred age of education was 14 years old. In an earlier study, Sawyer et al. (2001) published that healthcare professionals feel it is most appropriate to discuss infertility at 13 years of age, although most report delaying this discussion until 15 years of age. Less than one third of our respondents reported learning about infertility in the age range that encompassed these previously established ages. Most participants in our study recall learning this information from a healthcare professional. However, no respondents were educated by a healthcare professional before the age of 10 years old, but there were instances of participants learning this information independently before the age of 10. Together, these findings indicate that men in our sample recall being educated later than they may have desired and later than healthcare professionals feel is appropriate. This illustrates the need for standardized guidelines for educating male patients with CF about infertility at an age that is thought to be beneficial by both patients and physicians.

Our finding that all individuals who were diagnosed before one year of age recall their education about possible infertility may be expected if the individuals are being followed regularly throughout childhood and early adolescence by healthcare professionals who specialize in CF and are aware of the importance of educating young men about possible infertility. In formulating recommendations about how and when to inform males with CF about possible infertility it will be important to consider the age at which individuals are diagnosed. If a patient is diagnosed after the recommended age for disclosing fertility information, it is important to ensure that the individual still receives appropriate fertility counseling. Regardless of age at diagnosis, our findings indicate that it is important to repeat and present this information more than one time; this would likely increase rates of recall.

2.5.2 Fertility Testing

About half of our participants reported that they had a clinical sperm count completed. Although this is a high percentage of men, when considering the population that is likely to have interest in participating in this research project, this is not surprising. Sawyer et al. (2005) found a similar rate of semen analysis for men with CF in their study. Among total participants in our study, 41 (55%) indicated that they currently desire a biological child in the future. Nearly half of these men had previously completed a clinical sperm count and reported a result of low or no sperm, confirming their infertility. These men would need to use Assisted Reproductive Technology (ART) to conceive a biological child.

One eighth of men in our study who have completed a semen analysis reported a typical sperm count, which is higher than the historically reported fertility rate of 2-3% (de Souza et al., 2018). Although unexpected, there are several explanations for this. The first possible explanation is that historically published fertility rates may underestimate the true prevalence of fertility in men with CF, especially in the context of nonclassical CF. There is also the possibility that these may have been fraudulent responses that were not filtered. A third explanation is that some of these men misunderstood or misreported the results of their clinical sperm count.

Although age and relationship status clearly influence the desire to have a child in the future, being single also does not eliminate the desire to have a child in the future. The desire for children can change overtime. Sawyer et al. (2005) found that most men with CF desired fertility testing prior to the age of 20, which is generally thought to be earlier than the age of partnering for most people. The age at which semen analysis took place was not evaluated by our survey; however, the current age of our participants who have not had semen analysis may indicate that men should be offered this testing earlier. The feeling that semen analysis should be offered sooner was also expressed by participants in the phone interviews. One participant clearly stated he would have completed some kind of fertility testing “in [his] early 20s” if it were available.

The means by which men obtained a sperm count was not evaluated. It is possible that healthcare providers could include information on the SCFT when discussing options for accessing fertility. Although the SCFT can be an affordable

or timely alternative, it should not replace clinical testing. In some instances, SCFT may be an appreciated resource for patients. Future studies may consider examining if fertility testing is routinely offered or if it generally happens at the request of the patient. It is possible that fertility testing is delayed for men with CF due to the average age that fertility testing is thought to be appropriate for the general population. Most individuals undergo fertility testing after failed attempts to conceive naturally, typically for one year; this protocol is clearly not appropriate for men with CF.

2.5.3 Desire for Children

Overall, the majority of men in our study expressed a desire for children in the future. Men who had taken modulators were much more likely to report that they desire a child in the future despite the fact that modulators are not expected to alter the infertility of men with CF, which is typically caused by irreversible CBAVD. Studies that were done prior to modulator therapy found that lung function was not directly related to the importance of having a child and self-reported health status was also unrelated to wanting a child (Fair et al., 2000; Sawyer et al., 2005). While the men in our study who had taken modulators reported wanting a child in the future at similar rates to men in previous studies, men in our study who had not taken modulators reported much lower rates of wanting a child. Our study did not specifically elicit reasons that participants do or do not desire a child, which may be a topic for future research. It is possible that, as more modulator treatments become available improving the quality of life and extending life expectancy for patients, more men with CF will want to explore the

possibility of fatherhood. This could be because of a reduction in perceived risk of morbidity and mortality for men with CF whose symptoms are improved while taking modulators.

Interestingly, more participants agreed with the statement “I want/wanted biological children” than those who indicated they want a child in the future. This indicates that the desire for children can change over time making it important to offer a balanced education to all men with CF regardless of current plans for children.

Three participants (5%) indicated that they would like to have a child via sperm donation; one of these men had not yet had a clinical sperm count. These same three participants indicated that they would also consider adopting a child in the future. A total of six men (8%) indicated that they would like to adopt a child in the future, with half exclusively considering adoption in order to parent a child. It is possible that men may want to exclusively adopt for many reasons. The sample size limits further analysis on this concept, but this may indicate that there are additional variables contributing to family planning preferences that were not measured. These may include feeling drawn to the concept of adoption independent of any CF related factors or may be related to other health problems caused by CF. Together, these findings indicate that family planning is fluid and changes over time. Fertility education should include discussion about family building options as well as clinical fertility testing.

2.5.4 Outlook on Fertility

Although source of education did not have a significant role in perception of infertility, the ethos of the information source has not previously been considered for effectiveness of fertility counseling in males with CF, to our knowledge. In contrast to perception of infertility, anxiety levels varied based upon the recalled source of education for men with CF on infertility. Men who reported learning of possible infertility independently indicated that they felt the most worry or anxiety about being potentially unable to father a biological child when compared to all other respondents. Strikingly, men who recalled being educated by a family member, typically their mother, reported the least anxiety about infertility. Anxiety levels did not seem to differ significantly based on current age groups or the age at which men were educated on infertility. This may indicate the need for collaborative counseling by both healthcare professionals and family members.

Embarrassment was also measured to evaluate the outlook of respondents and compared based on the person who educated the men about infertility. Nearly half of respondents reported having felt embarrassed about the possibility of infertility and some reported avoiding disclosing fertility information to romantic partners. Similar to feelings of anxiety, participants who learned of infertility independently reported higher frequencies of feeling embarrassed about the possibility of being infertile. Sawyer et al. (2001) found that many healthcare providers delay education about possible infertility due to potential embarrassment. Our findings do show that some patients feel embarrassed

about possible infertility; however, this does not depend on source of infertility education. Future studies may consider specific methods for or approaches to fertility counseling for adolescents that may reduce embarrassment.

2.5.5 Birth Control Practices

The level of how responsible respondents felt to prevent a pregnancy was also evaluated. Most participants who feel no obligation to use birth control indicated that they also do not rely on their partner to prevent pregnancy. Additionally, the majority of men who had not yet had a clinical sperm count indicated that they do not feel obligated to use birth control to prevent pregnancy. These men may be using assumed infertility as a means of preventing an unplanned pregnancy.

In order to better understand birth control practices of men with CF, we compared their perceptions of infertility with their feelings of responsibility to use birth control and their use of condoms. Nearly three-quarters of heterosexual participants who reported feeling infertile agreed that their understanding of CF associated infertility affected their use of birth control. The questionnaire did not ask participants to specify how infertility changed their birth control practices. However, the majority of those who indicated they do not feel obligated to use birth control to prevent pregnancy indicated that they also do not rely on their partner to prevent pregnancy.

When asked about condom use, 69% of participants reported using condoms in the past, for either pregnancy prevention, sexually transmitted infection (STI) protection, or both. The results of our study appear to be

consistent with Sawyer et al. (2005) who found that a third of their participants felt they did not need to use a condom due to their likelihood of being infertile. Additionally, there are many other reasons men may decide to not use a condom during sexual intercourse. Future studies could consider exploring specific birth control methods used among men with CF. Condoms are the only form of birth control that also decreases the risk of being infected with a STI. Although it is important that men with CF do not rely on unconfirmed fertility status as birth control, fertility counseling could also be an important opportunity for healthcare providers to educate their patients about the use of condoms to prevent STIs.

Perceptions of family planning and perceptions on birth control are related but distinct concepts. An individual's perception of family planning can be thought of as the steps they would take to grow their family, while an individual's perception of birth control can be thought of as the steps they would take to avoid growing their family. Less than one third of respondents indicated that their perception of their fertility changed both their plans to have children and their plans to avoid having children while only a few indicated that their understanding of their fertility changed neither their plans to have children or prevent pregnancy. This may be affected by their desires to have or not have children. However, two thirds of participants indicated that their understanding of their fertility only affected their perception of family planning or only affected their use of birth control. This may reflect imbalances in their education. Family planning and birth control should both be discussed equally during educational counseling on fertility.

2.5.6 Strengths and Limitations

This study explored a novel concept in the target population of men with CF receiving care in the US. Even globally, few studies have been done that specifically look at the attitudes of men with CF surrounding fertility and birth control. When considering the recent advances in care for men with CF, this study is essentially the first of its kind in the new era of *CFTR* modulators. Additionally, this study looked at many other factors that may influence how men feel about fertility.

Sexual orientation information collected on respondents was used to evaluate their use of birth control and condoms for the purpose of pregnancy prevention. It may have been better to ask about past sexual encounters specifically. Men who indicated they were exclusively attracted to other men were not presented with the questions used to evaluate birth control practices; however, it may not be appropriate to assume that they have never had a sexual encounter with a female. Additionally, men who reported they were attracted to women were asked these questions without determining if they had ever been sexually active. More than half of our respondents indicated they were in a long-term relationship or married; asking about their current and historic birth control practices separately may have been more informative due to possible discontinued condom use in a committed relationship (Reece et al., 2010).

This study was limited by a small, convenient sample obtained from Facebook and, unfortunately, some data integrity may have been lost due to fraudulent responses. We were unable to perform a comprehensive qualitative

analysis, limited by number of participants. This is, however, an important goal for future work. Lastly, the goal of this project was to describe and better understand the factors effecting the outlook on fertility and birth control use in men with CF; in the future, it may be important, in larger samples, to use advanced statistical techniques to better understand nuances of the experiences of men with CF around fertility.

Further, it is unclear if our participant population reflects that of the broader population of men with CF. Several differences in our data and the data published by the Cystic Fibrosis Patient registry were noted (CFF, 2021). For example, the demographic information collected from the survey participants was unexpected and not consistent with population rates of CF across racial and ethnic groups. Approximately one fifth of participants reported their race to be black or African American. In comparison to the Cystic Fibrosis Foundation Patient registry published in 2021 which reported 4.7% of patients with CF were African American, this is a much larger portion of our sample than we would expect (CFF, 2021). There is a possibility that this could be the result of a small sample size or reflect the cultural identity of respondents rather than their ancestry. The demographics of each Facebook group used to distribute the survey are not known but may explain this finding as well. Our study was also limited by self-reported genotype data. The four most common variants reported by our survey respondents were in alignment with the four most common variants in the Cystic Fibrosis Patient registry (CFF, 2021). However, while only 59% of survey respondents indicated they had at least one F508del, the Cystic Fibrosis

Patient registry reports that 85.8% of those affected by CF carry at least one F508del variant. This may be a result of the small sample size, participants only reporting one variant, or not knowing their genotypes at all. Another discrepancy from the Cystic Fibrosis Patient registry was observed when assessing data about pancreatic insufficiency. Although pancreatic insufficiency was reported by nearly three quarters of participants in the current study, the Cystic Fibrosis Patient registry published that 83.8% of patients utilized pancreatic enzyme replacement therapy (CFF, 2021). Similarly, the patient registry reported that the majority of individuals over the age of 12 years old (82.3%) were prescribed a modulator therapy (CFF, 2021). Approximately half of our respondents indicated that they had ever taken modulator therapy. There are obstacles and barriers to receiving modulator therapy, such as insurance coverage, not having an eligible genotype, financial hardship, side effects, or not being seen by a CF specialist regularly who may be familiar with CF treatments. However, this is much lower than would be expected in a truly representative sample of men with CF.

2.5.7 Future Directions

This study provides important background for future studies exploring male fertility in CF. Replicating this study with refined survey questions and confirming genotypes with a larger sample size could provide a clearer picture of our current findings. Additionally, a study that takes place over a longer period of time, developed to understand how outlook on family planning changes over a lifetime for men with CF may also yield important information for making changes in how men with CF are counseled on fertility. Focus groups consisting of

healthcare providers, parents, and adult males with CF may be useful to determine the most beneficial ways for parents and healthcare providers to work collaboratively for the benefit of adolescent males with CF.

A larger study utilizing an at-home fertility test may also provide updated information for men with CF and their providers. In the future, the use of SpermCheck® Vasectomy Home Test for Men may be a more useful tool for researchers than the SCFT utilized in the current study. The SpermCheck® Vasectomy Home Test for Men detects a sperm concentration of 250,000 sperm/mL and above, which may be more useful for detecting CBAVD. Future studies may also consider comparing experiences with at-home tests to experiences of clinical fertility testing.

2.6 Conclusion

Most men in our study accepted and understood the likelihood that they may be infertile regardless of their recalled source of education about infertility. A large majority of participants reported learning about CF associated infertility between the ages of 10 and 20 years old, usually from a healthcare provider. There may be an impact on anxiety and embarrassment about infertility based on when men learn about possible infertility and their source of that information. Men who learned about infertility without professional or other outside guidance were found to be more anxious and embarrassed than men who learned about possible infertility from family or healthcare providers.

The majority of participants in this study indicated having a desire for a future child at some point over their lifetime and some participants reported that

they have already become a parent. More men who had taken modulators expressed a desire for a child in the future than those who had not taken modulators, despite the fact that modulator use does not reverse CBAVD, the most common cause for infertility in men with CF. This difference in desire may be related to their outlook if they experience increased quality of life and improvement of symptoms while taking modulators.

When considering mode of conception, some men in our study were open to alternative family building methods such as donor sperm or adoption. Younger men and men who were single reported desire for future children at lower rates than their older, partnered counterparts. This suggests that desire for children is dynamic, changing situationally and over time.

Previous clinical fertility testing was also reported by more than half of participants. While most reported below average sperm count, as is expected, some reported normal sperm count. This underscores the need to offer fertility testing or ultrasound to confirm the absence of the bas deferens as intact fertility may be underestimated in men with CF.

Fertility testing is important for men with CF not only when considering building their family, but also when considering options for family planning, especially because some men in our study reported intact fertility. Those who believe they are infertile are less likely to see a need for birth control. Although many participants reported using condoms in the past, some did not. Condoms are the only form of birth control that prevents the transmission of STIs and

fertility education and counseling for young men with CF may be an important education opportunity to discuss the importance of condom use.

When using the at-home fertility test as part of the current study, men reported a favorable experience and all of them felt that an at-home testing method should be offered to other men with CF. Reactions included initial sadness for some, but all reported feeling relief that their suspected infertility was now confirmed. Less uncertainty about their fertility status offered some of the participants closure as well as information to discuss with their partners. Participants also reported frustration regarding the lack of resources about CF associated infertility and fertility testing options.

As for all individuals, there are many factors that affect the desire to have or not have children for men with CF. Beyond personal preference, we identified the counseling these men receive as an important factor that alters their thoughts and feelings about family planning and birth control. More research needs to be done to determine when, how, and by whom males with CF should receive fertility information.

CHAPTER 3

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APPENDIX A

SURVEY

Cystic Fibrosis Fertility Status and Outlook

Thank you for your interest in participating in this research study! In this study, researchers with The University of South Carolina, and collaborators a The Medical University of South Carolina, hope to gather information about how counseling on fertility has affected men with Cystic Fibrosis regarding family planning and birth control practices.

This survey will take approximately 20 minutes. In order to be eligible for this study, you must be 18 years old or older, assigned male at birth, and have Cystic Fibrosis. This survey is completely voluntary and can be stopped at any time without consequence. Your responses are anonymous and no identifying information will be shared or published. By continuing, you are consenting to participating in this part of this research study.

If you have any questions, please contact:

Allison Szczepanski

(XXX) XXX-XXXX

allison.perez@uscmed.sc.edu

Captcha Check Point

Demographics

1. What is your age? _____
2. Select your race (select all that apply)

    White or Caucasian

    Asian

    Black or African American

    American Indian or Alaska Native

    Native Hawaiian or other Pacitic Islander

    Other

3. Select your ethnicity

    Hispanic or Latino

    Not Hispanic or Latino

4. Sex assigned at birth

    Male

    Female

5. My gender identity is…

    Man

    Woman

    Non/binary/third gender

    Prefer not to say

6. I am sexually attracted to… (select all that apply)

    Men

    Women

    Non-binary/ third gender

7. My relationship status is…

    Single

    In a long-term, committed relationship

    Married

    Other

CF History

8. At what age were you diagnosed with Cystic Fibrosis?

    Less than 1 year old

    Between 1 and 9 years old

    Between 10 and 19 years old

    20 years old or older

9. What *CFTR* variants (mutations) cause your Cystic Fibrosis (please select up to two)

    F508del

R117H

G542X

G551D

N1303K

621+1G>T

R553X

Something not listed here

I have the same mutation twice (homozygous)

I don't know my mutation(s)

Display this question if "Something not listed here" is selected:

What *CFTR* variants (mutations) cause your Cystic Fibrosis?

10. Are you pancreatic insufficient? (Do you take pancreatic enzymes?)

No

Yes

11. Have you ever taken a modulator? (Symdeko, alydeco, Orkambi, Trikafta, or others)

Yes

No

Display this question if "yes" is selected:

Please explain your history with modulators briefly. What are you taking, for how long, and what have you taken previously?

_____
_____
_____

12. Have you learned about possible infertility for men with Cystic Fibrosis?

Yes

No

Display this question if “yes” is selected:

At what age did you learn about possible infertility?

Less than 10 years old

Between 10 and 15 years old

Between 16 and 20 years old

21 years old or older

Display this question if “yes” is selected:

Who taught you about possible infertility?

_____

_____

13. Have you ever completed a sperm count in a fertility clinic?

Yes

No

I am not sure

Display this question if “yes” is selected:

What were the results of your sperm count?

Normal range

Low sperm count

No sperm

Number of Children: Current and Future

14. How many children do you have? (fill in number values)

Biological ___

Donor conceived ___

Adopted ___

Step ___

Unknown (I am unsure if I am the father) ___

Total number of children ___

15. In the future, how many children would you like to have? (fill in number values)

Biological ___

Donor conceived ___

Adopted ___

Step ___

Total number of children ___

Fertility

Please indicate how much you agree with the following statements

16. I do/would enjoy some or all aspects of being a parent.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

17. I want/wanted biological children.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

18. I feel that I am likely infertile.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

19. I feel that my perception of my fertility has affected my family planning.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

20. I have felt worried that I would not be able to father a biological child.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

21. I have felt worried about how my fertility may affect my romantic relationships.

    Strongly Agree

    Agree

Neutral

Disagree

Strongly Disagree

22. I have avoided disclosing information about my fertility to romantic partners in the past.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

23. I have felt embarrassed about the possibility that I may be infertile.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

24. I think infertility is a significant burden of Cystic Fibrosis.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

Family Planning

Display this question if “Women” is selected for question 6

25. My knowledge or perceptions of infertility have changed my personal use of birth control methods, including condoms, in the past.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

26. I do not feel obligated to use birth control or condoms for the purpose of preventing pregnancy because of my assumed fertility status.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

27. I have used condoms in the past, but only for prevention of STIs.

    Strongly Agree

    Agree

    Neutral

    Disagree

    Strongly Disagree

28. I have used condoms in the past, to prevent STIs and pregnancy.

    Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

29. I rely on my partner to take responsibility to prevent pregnancy.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

30. I have felt worried my partner may become pregnant unexpectedly in the past.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

31. I think that probable infertility is a "silver-lining" of having Cystic Fibrosis.

Strongly Agree

Agree

Neutral

Disagree

Strongly Disagree

Interest in Part Two of Study

32. For the second part of this study, 10 participants can receive a free at-home SpermCheck® Fertility Test kit and share their experience with the test over the phone. Are you interest in learning more about participating in the second part of the study?

    Yes

    No

    Display this question if “yes” is selected:

    Please enter your phone number if you would like to learn more about the next part of this study. By entering your phone number you are agreeing to be contacted by the primary investigator of this study.

    _____

    Display this question if “yes” is selected:

    Please enter your name. By entering you name you are agreeing to be contacted by the primary investigator of this study.

    _____

APPENDIX B

RECRUITMENT FLYER

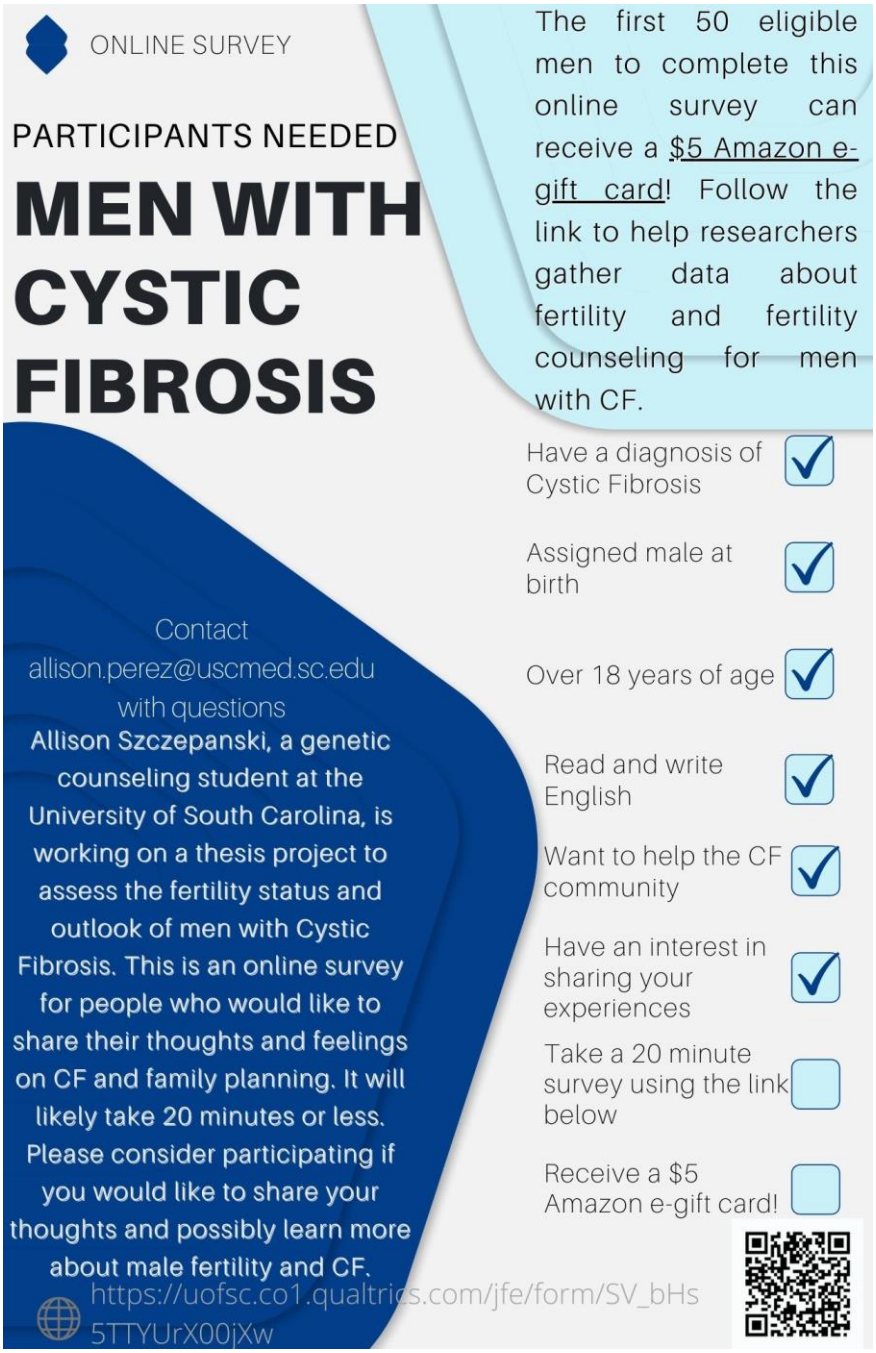

Figure B.1 Recruitment Flyer

APPENDIX C

OPTIONAL GIFT CARD QUESTIONNAIRE

Gift Card Information

Captcha Checkpoint

The information you enter here is sperate from your answers on the previous survey. The information you enter in this survey will be used to contact you.

1. Would you like to receive a $5 Amazon girl card for your time? (subject to availability)

    Yes

    No

        Display this question if “yes” is selected:

        Please enter your email address to receive a $5 Amazon e-gift card (subject to availability)

        _____

APPENDIX D

INITIAL PHONE CALL SCRIPT

Hello, my name is Allison Szczepanski. Am I speaking with [NAME PROVIDED BY PARTICIPANT]?

Yes: *continue on*

No: Do you know when he may be available for a phone call? *Plan to call back at that time*

I am calling to follow up about the survey you took for men with Cystic Fibrosis. I am a genetic counseling graduate student at The University of South Carolina's school of medicine. I am in South Carolina undertaking research that will be used in my thesis. This phone call is being recorded. Do you agree to this being recorded?

Yes: *continue on*

No: Thank you for your time.

I am studying fertility outlook and status of men with CF. Thank you for the information you provided in the online survey on [DATE OF SURVEY TAKEN]. You indicated that you may be interested in the second part of my study, so I wanted to reach out and give you more information for the consenting process. Are you still interested?

Yes: *continue on*

No: Thank you for your time.

There are a couple of points I will need to cover with you.

The next step in this research is exploring the rates of fertility in men with CF. This will include participants taking an at home SpermCheck® test which will be sent to their homes free of charge. Instructions will be included with the test kit for review, but this would involve the participant providing a semen/ejaculate sample and then placing it on the SpermCheck® device. After seven minutes, the test would then indicate the presence or absence of sperm in the semen. In order for the test to be accurate, the user must have ejaculated within the last week, but not within the last two days prior to testing. In other words, the user cannot have ejaculated within the last two days but must have ejaculated within the last 7 days. Ejaculation must occur between 7 and 3 days prior to testing to ensure

accuracy of testing. This is only one measure of fertility and therefore it cannot be considered a full fertility work up. Additionally, fertility status can change over a person's lifetime for many reasons.

If you decide to take part in this project, a time would be scheduled to speak on the phone again within the two days after the test is completed. During that phone call, you would be asked several questions about your experience using the test and about the results. This phone call would take approximately 15 minutes.

The information provided during this conversation would be used to evaluate the ways that men are currently counseled on fertility, how counseling methods could be improved, how accurate the current estimates of fertility in men with CF are, and determine if the SpermCheck® test may be useful for other men with CF.

All efforts will be made to keep the provided information and the results of the test in the strictest confidentiality, but there is always a small chance of a breach of confidentiality. Your name will not be linked to any of the data provided for the study or any publication. The de-identified information may be used for publication or shared with other researchers without additional consent from the participants.

There is a chance that taking this test and hearing these questions during the phone interview may make you feel unexpected emotions. Additionally, learning that there is or is not sperm present in the ejaculate may make a participant feel unexpected emotions.

Participation is voluntary. There will be no penalty or loss of benefits to which the individual is otherwise entitled if the decision to not participate is made. You can decline to answer any question; as well as to stop participating at any time, without any penalty. This study has been approved by the University of South Carolina internal review board.

The interview during the second part of the research, would be recorded in order to ensure an accurate record of the information provided. The recording will be transcribed by hand and the transcripts will be kept confidential and secured. The recording will be erased after it is transcribed.

Do you have any questions about this research?

If you have any questions concerning this research in the future, please feel free to contact me at any time. My contact information can be found on the post for the original survey, the informed consent form, or I can repeat it now:

Allison Szczepanski

(XXX) XXX-XXXX

allison.perez@uscmed.sc.edu

Would you like to participate in the second part of this study?

Yes: please provide your email address so that I may email you the official informed consent form. *Participant gives email address*

Once I receive your signed consent form via email, I will call back to get your mailing address and at that time we can schedule a time for the phone interview about your results.

No: Thank you for your time.

APPENDIX E

CONSENT FORM

UNIVERSITY OF SOUTH CAROLINA
CONSENT TO BE A RESEARCH SUBJECT
Fertility Status and Outlook of Males with Cystic Fibrosis

KEY INFORMATION ABOUT THIS RESEARCH STUDY:

You are invited to volunteer for a research study conducted by Allison Perez Szczepanski. I am a graduate student in the School of Medicine Genetic Counseling Program, at the University of South Carolina. The University of South Carolina Genetic Counseling Program and The Medical University of South Carolina Cystic Fibrosis Center are sponsoring this research study. The purpose of this study is to evaluate perceptions of fertility and sexual health practices in males with Cystic Fibrosis, evaluate patient experience using a SpermCheck® home fertility test, and compare fertility outlook before and after receiving results from the SpermCheck® home fertility test. Typically, males with CF are quoted historic fertility data that suggest only 2 to 3% of men with CF are fertile. This data has been collected over decades of research, but very few studies have focused specifically on fertility as it relates to genotype. These studies documented that the infertility seen in males with CF is caused by congenital bilateral absence of the vas deferens (CBAVD). Although there are many other factors related to male fertility, presence of sperm in ejaculate is an indicator that the vas deferens are not absent and fertility may not be disrupted. You are being asked to participate in this study because you participated in the first part of this study and indicated that you would be interested in participating in part two. This study is being done at The University of South Carolina and will involve approximately ten volunteers.

The following is a short summary of this study to help you decide whether to be a part of this study. More detailed information is listed later in this form.

The next step in this research is exploring the rates of fertility in men with CF. This will include participants taking an at home SpermCheck® test which will be sent to their homes free of charge. Instructions will be included with the

test kit for review, but this would involve the participant providing a semen/ejaculate sample and then placing it on the SpermCheck® device. After seven minutes, the test would then indicate the presence or absence of sperm in the semen. In order for the test to be accurate, the user must have ejaculated within the last week, but not within the last two day prior to testing. In other words, the user cannot have ejaculated within the last two days but must have ejaculated within the last 7 days. Ejaculation must occur between 7 and 3 days prior to testing to ensure accuracy of testing. This is only one measure of fertility and therefore it cannot be considered a full fertility work up. Additionally, fertility status can change over a person's lifetime for many reasons.

If you decide to take part in this project, a time would be scheduled to speak on the phone again within the two days after the test is completed. During that phone call, you would be asked several questions about your experience using the test and about your results. This phone call would take approximately 15 minutes.

The information provided during this conversation would be used to evaluate the ways that men are currently counseled on fertility, how counseling methods could be improved, and determine if the SpermCheck® test may be useful for other men with CF.

All efforts will be made to keep the provided information and the results of the test in the strictest confidentiality, but there is always a small chance of a breach of confidentiality. Your name will not be linked to any of the data provided for the study or any publication. The de-identified information may be used for publication or shared with other researchers without additional consent from the participants.

There is a chance that taking this test and hearing these questions during the phone interview may make you feel unexpected emotions. Additionally, learning that there is or is not sperm present in the ejaculate may make a participant feel unexpected emotions.

Participation is voluntary. There will be no penalty or loss of benefits to which the individual is otherwise entitled if the decision to not participate is made. You can decline to answer any question; as well as to stop participating at

any time, without any penalty. This study has been approved by the University of South Carolina internal review board.

PROCEDURES:

If you agree to participate in this study, you will do the following:

1. Return this signed consent form to the primary investigator by emailing it to allison.perez@uscmed.sc.edu (a picture of the signed consent form is sufficient)
2. Schedule a phone interview for after you have completed the test and provide your mailing address.
3. Receive an at home SpermCheck® test via US postal service.
4. Complete the SpermCheck® test according to the instructions included in the box.
5. Take part in a 15-minute phone interview with the primary investigator. This interview will be recored in order to ensure the details that you provide about your testing experience are accurately captured.

DURATION:
Participation in the study involves using an at home SpermCheck® test and then participating in a phone interview that is expected to last about 15 minutes.

RISKS/DISCOMFORTS:

There is a chance that taking this test and hearing these questions during the phone interview may make you feel unexpected emotions. Additionally, learning that there is or is not sperm present in the ejaculate may cause you to feel unexpected emotions.

There is the risk of a breach of confidentiality, despite the steps that will be taken to protect your identity. Specific safeguards to protect confidentiality are described in a separate section of this document.

BENEFITS:

You may benefit from participating in this study by receiving a free SpermCheck® test kit.

COSTS:

There will be no costs to you for participating in this study.

PAYMENT TO PARTICIPANTS:

You will not be paid for participating in this part of this study.

CONFIDENTIALITY OF RECORDS:

Information obtained about you during this research may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The investigators associated with this study, the sponsor, and the Institutional Review Board will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law. Study information will be securely stored on password-protected computers.

VOLUNTARY PARTICIPATION:

Participation in this research study is voluntary. You are free not to participate, or to stop participating at any time, for any reason without negative consequences. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner. If you wish to withdraw from the study, please call or email the principal investigator listed on this form.

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. **If I have any more questions about my participation in this study, or a study related injury, I am to contact Allison Perez Szczepanski at (XXX) XXX-XXXX or email allison.perez@uscmed.sc.edu.**

Concerns about your rights as a research subject are to be directed to, Lisa Johnson, Assistant Director, Office of Research Compliance, University of South Carolina, 1600 Hampton Street, Suite 414D, Columbia, SC 29208, phone: (803) 777-6670 or email: LisaJ@mailbox.sc.edu.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Subject / Participant	Date
Signature of Qualified Person Obtaining Consent	Date

APPENDIX F

SCHEDULING PHONE CALL SCRIPT

Hello, my name is Allison Perez Szczepanski. Am I speaking with [NAME PROVIDED BY PARTICIPANT]?

Yes: *continue on*

No: Do you know when he may be available for a phone call? *Plan to call back at that time*

I am calling to let you know that I received your signed consent form for the second part of my study for Men with Cystic Fibrosis. Do you agree to this being recorded?

Yes: *continue on*

No: Thank you for your time.

Do you still wish to participate in this research?

Yes: *continue on*

No: Thank you for your time.

In that case, I will need your mailing address so that I can send the testing kit to you. What is your mailing address?

Participant provides mailing address

We will now schedule a time that we can speak after you complete the kit. The timing of the sample is important in providing the most reliable results from the home sperm test. Abstinence from ejaculation for at least 48 hours before taking the test is required for the test to work, but there must be ejaculation occurring within at least 7 days before the test. With that in mind, what days and times in the coming weeks would work well for your schedule. I would like to speak with you no more than 2 days after you complete the test.

Schedule a time

I look forward to speaking with you then. If you have any questions, please do not hesitate to reach out to me. Thank you for your time.

APPENDIX G

EMAIL INCLUIDNG MOCK SCHEDULE

Hello [PARTICIPANT NAME],

Below is a calendar for your testing schedule and a brief overview of instructions for completing the test kit. I have also attached some directions from the testing company.

Sun	Mon	Tues	Wed	Thurs	Fri	Sat
1/**	1/**	1/**	1/**	1/**	1/** Call to schedule interview	1/**
1/**	1/**	1/** No Ejaculation	1/** No Ejaculation	1/** Test estimated to arrive. Complete test.	1/** Phone interview at 5:00 PM	1/**

Instructions at a glance:

1. Wait at least 2 days (but not more than 7 days) since last ejaculation
2. Ejaculate into the cup provided in the test kit- it is important to collect all of the ejaculation in the cup
3. Wait 20 minutes
4. Stir liquid with transfer device included with kit
5. Transfer the specified volume (fill the dropper to the frosted line) of liquid into the bottle with the purple top
6. Turn the bottle upside down 5 to 10 times
7. Wait 2 minutes
8. Put exactly 6 drops of the liquid in the bottle onto the SpermCheck device
9. Wait 7 minutes
10. Read results

I look forward to speaking with you next Friday. Please contact me with any questions or concerns.

Best,

Allison Szczepanski

Genetic Counseling Candidate

University of South Carolina

School of Medicine

allison.perez@uscmed.sc.edu

(XXX) XXX-XXXX

APPENDIX H

SpermCheck® INSTRUCTIONS

QUICK GUIDE TO PERFORMING THE SPERMCHECK FERTILITY TEST

Be sure to read ***How to Perform the Test*** on Page 2 of these instructions before beginning the test.

1. Let semen stand for twenty (20) minutes.
2. Punch out perforated circle on box and insert Solution Bottle so that it stands upright.
3. Use Semen Transfer Device to gently stir and mix semen in Semen Collection Cup.
   Pull plunger to draw semen up to the bottom of the raised frosted line.
4. Remove purple cap from Solution Bottle.
5. Add semen from Semen Transfer Device to Solution Bottle.
6. Replace purple cap. Mix gently by inverting bottle several times.
7. Wait two (2) minutes.
8. Unscrew clear tip from Solution Bottle cap.
9. Add six (6) drops into oval sample-well marked "S".
10. Begin timing and wait seven (7) minutes.
11. Read result at exactly seven (7) minutes.

SpermCheck Fertility Helpline
(866) 635-2308 Weekdays 8:30 AM to 5:30 PM Eastern Time
Visit us at SpermCheckFertility.com

4

INTERPRETATION OF TEST RESULTS

Positive (Normal): If you see both a Control Line (marked as "C" on the SpermCheck Device) and a Test Line (marked as "T" on the SpermCheck Device), your sperm count is at least 20 million per milliliter, which is considered a healthy threshold for male fertility. **IMPORTANT:** The test line does not have to be as dark as the control line. *Even a very faint test line is a high result.*

Negative (Low): If you see a Control Line (marked as "C" on the SpermCheck Device) but not a Test Line (marked as "T" on the SpermCheck Device) your sperm count is less than 20 million per milliliter.

Invalid: If you do not see a control line (marked as "C" on the SpermCheck Fertility Device) the test cannot be interpreted and you should test again with another SpermCheck Fertility Device.

- For in vitro diagnostic use. Not to be taken internally.
- Store in a dry place between 36°F - 86°F (2°C - 30°C).
- DO NOT FREEZE.
- Protect from sunlight.
- Read the instructions carefully and completely before starting the test.
- Do not use after the expiration date printed on the package.
- This test is intended for a single use only. DO NOT RE-USE.

Manufactured by PBM
Princeton BioMedtech Corp.
4242 US Highway 1
Monmouth Junction, NJ 08852
U.S.A.
Tel: +1 732-274-1000

Printed in U.S.A. 10/20/2011

Distributed by
DNA Diagnostics Center®
1 DDC Way Fairfield, OH 45014
U.S.A.SpermCheckVasectomy.com

P-5195-G

SpermCheck® FERTILITY

Instructions For Use

Home Sperm Test for Male Fertility

INDICATIONS FOR USE

SpermCheck Fertility is a fast at-home test to detect the concentration of sperm in semen. This simple test quickly lets you know whether your sperm count is considered within the normal range for a fertile male.

SpermCheck Fertility gives you either a positive (normal sperm count) or negative (low sperm count) result. Regardless of the test result, it is important that you fully understand what your test means before deciding whether or not to consult your physician. Use only in accordance with the instructions provided.

IMPORTANT INFORMATION ABOUT THIS TEST

- For in vitro diagnostic use.
- Not to be taken internally.
- Store in a dry place between 36°F - 86°F (2°C - 30°C). DO NOT FREEZE. Protect from sunlight.
- Read the instructions carefully and completely before starting the test.
- Do not use after the expiration date printed on the package.
- Keep out of the reach of children.
- Do not use this test as a method of birth control.
- This test does not protect against sexually transmitted diseases.
- This test cannot be used to prove paternity.
- Poor vision and/or improper lighting may affect interpretation of the results.
- This test is intended for a single use only. DO NOT RE-USE.
- This test assesses sperm concentration only. It does not detect all fertility issues.

MATERIAL WARNINGS AND PRECAUTIONS

All kit components are non-toxic and safe. The Solution may cause irritation if it contacts eyes; if it does, flush eyes with plenty of water. Dispose of any unused kit components in normal household waste when no longer needed.

- For in vitro diagnostic use.
- Not to be taken internally. Do not re-use.
- Store in a dry place between 36 - 86°F (2 - 30°C).
- Do not freeze. Protect from sunlight.

Use only in accordance with the following instructions.

INSTRUCTIONS FOR USE

For accurate results, you must follow the steps below as described in this instruction pamphlet.

1. Read and understand the entire instruction pamphlet.
2. Check the kit contents.
3. Collect a semen sample.
4. Perform the test.
5. Read the result.
6. Call your doctor, Customer Service at (866) 635-2308, or visit info@spermcheck.com if you are not sure how to perform the test, how to read the result, or if you don't understand the meaning of your test result.

KIT CONTENTS

Your SpermCheck Fertility Kit contains everything you need to perform one (1) SpermCheck Fertility test. Open the kit and make sure it contains the following items:

If any parts of the kit are missing or damaged, please return the kit to the place of purchase or contact Customer Service at (866) 635-2308 or info@spermcheck.com for assistance.

MATERIALS REQUIRED, BUT NOT PROVIDED

- Timer or watch

HOW TO COLLECT YOUR SEMEN SAMPLE

When collecting semen, wait at least 48 hours, but no more than seven (7) days, after your last ejaculation. Obtain your semen sample by manual stimulation (masturbation). Collect the sample in the Semen Collection Cup provided.

- **Ejaculate directly inside the Semen Collection Cup without losing any portion of the semen. It is important to collect the entire ejaculate.** *Do not use any lubricants or lotions since this may interfere with the test result. Do not use a condom to collect the sample.* If you do lose some of the semen, discard the sample, rinse the cup with tap water only, and let it air dry before using it again. Do not use soap or detergent to wash the cup. Wait at least 48 hours, and then collect a fresh sample for testing.
- After collecting the sample, let the cup stand upright on a flat surface.
- The semen should be tested within three (3) hours after collection.
- **When you are ready to test, follow the instructions in the next section, *How to Perform the Test*.**

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HOW TO PERFORM THE TEST

Have a watch or other timer ready before starting the test. Work on a flat surface.

1. **Let semen stand for twenty (20) minutes.**
   Semen is too thick to be tested immediately after ejaculation, so you must wait at least 20 minutes for semen to become thin (liquefy). Samples may be tested up to three (3) hours after collection. Discard sample if not tested within three (3) hours and wait at least 48 hours to obtain a fresh sample for testing.

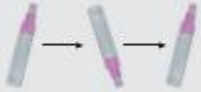
2. **Place all kit components on a flat surface within easy reach.**
3. **Carefully place Solution Bottle into Solution Bottle Stand.**
   Punch out round perforation located in the top-right corner on the side panel of the box. This creates a stand to hold the Solution Bottle. Unscrew purple cap on the Solution Bottle to remove the clear cap, and place bottle into the stand so it won't tip over.

4. **Fill Semen Transfer Device to the line.**
   Use Semen Transfer Device to gently stir and mix the semen sample in the Semen Collection Cup. Next, insert Semen Transfer Device into semen sample, avoiding any solid or sticky material. Slowly pull plunger to draw semen into Semen Transfer Device until semen level reaches the bottom of the raised frosted line.
   Avoid getting air bubbles in the Semen Transfer Device. If this occurs, push the semen back out of the Semen Transfer Device and then draw semen into the Semen Transfer Device again. Make sure the semen fills the Semen Transfer Device just to the bottom of the raised frosted line. Add or remove semen until it exactly matches the bottom of the raised frosted line on the Semen Transfer Device.

5. **Remove purple cap from Solution Bottle.**

6. **Add semen from Semen Transfer Device to Solution Bottle.**
   Insert the Semen Transfer Device into the Solution Bottle and gently press the plunger on the Semen Transfer Device to add the semen to the Solution Bottle.

7. **Replace purple cap on Solution Bottle and mix semen with the solution.**
   Screw the purple cap back onto the Solution Bottle and mix the contents by gently turning the Solution Bottle upside down several times. Do not shake vigorously as this will cause bubbles.



8. **Wait for two (2) minutes.**
   Place the Solution Bottle back in the Solution Bottle Stand. Leave it there for two (2) minutes before proceeding to the next step.

9. **Unscrew clear tip from Solution Bottle cap.**
   Remove the Solution Bottle from the Solution Bottle Stand, unscrew the small tip from the Solution Bottle cap, and discard the clear tip.

10. **Add six (6) drops from Solution Bottle to Sample-Well of the SpermCheck Fertility Device.**
    Lay the SpermCheck Fertility Device face up on a flat surface. Hold the Solution Bottle straight up and down over the sample-well of the device and squeeze gently to add exactly six (6) drops of Solution. The sample-well is marked with an "S" on the SpermCheck Fertility Device.

    Do not add more or fewer than six (6) drops to the SpermCheck Fertility Device sample-well.

11. **Begin timing and wait seven (7) minutes.**
    Begin timing after adding the Solution to the sample-well.

12. **Read the result at precisely seven (7) minutes. See page 3 for details, under *How to Read the Test Results*.**
    Do not read the test result earlier or wait longer than seven (7) minutes as this may produce an incorrect result.

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HOW TO READ THE TEST RESULTS

Read the test in a well-lit area. If you know you have poor vision, you may want to have someone help you read the test.

Positive (Normal): If you see both a Control Line (marked as "C" on the SpermCheck Device) and a Test Line (marked as "T" on the SpermCheck Device), your sperm count is at least 20 million per milliliter, which is considered a healthy threshold for male fertility. **IMPORTANT:** The test line does not have to be as dark as the control line. *Even a very faint test line is a positive result.*

Negative (Low): If you see a Control Line (marked as "C" on the SpermCheck Device) but not a Test Line (marked as "T" on the SpermCheck Device) your sperm count is less than 20 million per milliliter.

Invalid: If you do not see a control line (marked as "C" on the SpermCheck Fertility Device) the test cannot be interpreted and you should test again with another SpermCheck Fertility Device.

THINGS THAT CAN CAUSE INCORRECT RESULTS

- Not following instructions correctly.
- Reading the test too soon or too late. You must read the result seven (7) minutes after adding the Solution/semen mixture to the sample-well.
- Adding Solution/semen to a part of the SpermCheck Fertility Device other than the sample-well.
- Adding too much or too little of the Solution/semen mixture to the sample-well. You must add exactly six (6) drops from the Solution Bottle to the sample-well.
- Adding the Solution/semen mixture to the Device too soon. You must mix the semen and Solution well and let the mixture stand in the Solution Bottle for two (2) minutes after adding the semen to the Solution Bottle.
- Adding too much or too little semen to the Solution Bottle. Be sure to fill the Semen Transfer Device with semen exactly to the bottom of the raised frosted line.
- Not collecting or failing to collect initial drops of the ejaculate. This can affect the overall sperm concentration of the semen sample and lead to an incorrect result.
- Poor vision or poor lighting. These factors may affect your ability to read and interpret the test correctly.
- Using lubrication during masturbation. Both commercial and natural lubes can contaminate the semen sample.

FREQUENTLY ASKED QUESTIONS

Q1. How accurate is the test?
A1 In a clinical study comparing the results of the SpermCheck Fertility Test to the standard microscopic laboratory test, SpermCheck Fertility was over 98% accurate in identifying if semen samples contained more or less than 20 million sperm per milliliter.

Q2. What does a positive test result mean?
A2. A positive result indicates your sperm count is at least 20 million per milliliter, a level that is considered "normal" for fertile men. However, a positive SpermCheck Fertility test result by itself does not prove you are fertile since there are several other factors that can influence a man's ability to father a child. If you and your partner are unable to conceive a child after several months of trying, you both should have full fertility evaluations, even if your SpermCheck test result is positive.

Q3. What does a negative test result mean?
A3. A negative result indicates your sperm count is less than 20 million per milliliter, which is below that of most fertile men. However, some men with sperm counts below this level are still able to father children naturally. Your sperm count can vary from day to day, so it is possible that you might get a positive result if you were to wait a while and test again. We recommend that you talk to a doctor about your test result and have a complete semen analysis to determine just how low your sperm count is and whether you have any other sperm abnormalities that could affect your fertility status.

Q4. My semen sample did not become a thin liquid after 20 minutes. Can I still perform the test?
A4. Some semen samples do not liquefy as quickly or as fully as others. The SpermCheck device may still give an accurate result even if your sample does not completely liquefy. It is important that you have allowed the sample to stand for at least 20 minutes and mixed it as directed, avoiding any solid material when adding semen to the SpermCheck Solution Bottle. Letting it stand longer (up to three hours) may help it become more liquid. Keeping the semen near body temperature (but no warmer than 98°F) by carefully floating the cup containing the sample in a bowl of shallow warm water may also help the sample liquefy. DO NOT MICROWAVE. Fill the Semen Transfer Device with semen from the part of the sample where it is most liquid. If your sample has not liquefied at all, or if you cannot fill the Semen Transfer Device to the bottom of the raised frosted line without it clogging with solid or stringy material, you should discard the sample. Wait at least 48 hours and collect another semen sample.

Figure H.1 SpermCheck® Instructions

APPENDIX I

INTERVIEW PHONE CALL SCRIPT

Hello, this is Allison Perez Szczepanski. Am I speaking with [NAME PROVIDED BY PARICIPANT]?

Yes: *Continue on*

No: Do you know when he may be available for a phone call? *Plan to call back at that time*

I am calling for our scheduled phone interview regarding your participation in my research study for men with Cystic Fibrosis. Is now still a good time to talk for about 15 minutes?

Yes: Great

No: Have you completed your SpermCheck® fertility test kit?

Yes: When would be a better time for this phone call?

No: Do you still plan to complete the kit and participate in the phone interview?

Yes: *reschedule time*

No: Thank you for your participation in my study.

Have you completed your SpermCheck® fertility test kit?

Yes: As a reminder, this call is being recorded. I will delete this recording after our conversation is transcribed. Everything you say will be de-identified. You are able to opt out at any time, end the interview, or chose not to answer any question. This is completely voluntary. *Participant agrees*

No: Do you still plan to complete the kit and participate in the phone interview?

Yes: *reschedule time*

No: Thank you for your participation in my study.

If you have any questions about the fertility test you have completed, you can ask me any questions at any time, including after the completion of this study, or review your results with a health care provider.

I understand that the results of this test may have caused you to feel unexpected or negative emotions. If you would like to discuss these before we begin the interview, I am here to listen. I can answer any of your questions about the test and your results to the best of my abilities and I would be happy to help you in anyway I can. Is there anything you would like to share before we begin?

I have several questions to ask you, most of which are simple yes or no questions. If you need clarification at any time, please ask me.

Were the directions that came with the kit easy to follow? Yes or no.

No: please explain.

The results of the test could be: two lines indicating a typical sperm count, one line indicating a low sperm count, or no lines indicating an invalid test. What were your SpermCheck® fertility test results? Two lines, one line, or no lines?

Did you get the results you were expecting based on prior understanding?

No: How were your results different from what you expected?

Do you believe that these results are accurate? Yes or no.

Have you undergone previous fertility testing? Yes or no.

Yes: Do these results agree with your previous fertility testing? Yes or no.

In light of your results using this kit, do you believe the counseling about fertility in men with CF you previously received was accurate? Yes or no.

In part one of this study, you indicated that you would like to have *PARTICIPANTS ANSWER TO QUESTION 30 ON SURVEY (this question is about how many children they would like to have in the future- biological, donor conceived, adopted, step, and total number)*. Have these results changed your thoughts or goals for family planning? Yes or no.

Yes: In what ways?

Do you feel that the results of this test will change your birth control practices? Yes or no.

Yes: In what ways?

Do you feel that the results of this test have changed your outlook on your fertility? Yes or no.

Yes: In what ways?

Do you think access to this sort of test would be helpful to the CF community? Yes or no.

Are there other comments about your experience that you would like to share?

This concludes the phone interview. I appreciate your time in participating in my study. If you have any questions about this study in the future, please feel free to contact me.