Prenatal genetic testing for cystic fibrosis: a systematic review of clinical effectiveness and an ethics review

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Purpose: We aimed to assess the clinical value of prenatal testing for cystic fibrosis (CF) and whether ethical considerations would affect endpoint selection.

Methods: To determine effectiveness, we conducted a systematic literature review whose protocol outlined search strategies across eight databases, study inclusion criteria, and prespecified literature screening, data extraction, and synthesis processes. We conducted a scoping search on ethical considerations.

Results: The genetic test showed good diagnostic performance. A change in clinical management was observed: termination of pregnancy (TOP) occurred in most cases where two pathogenic variants were identified in a fetus of carrier parents (158/167; 94.6%). The TOP rate was lower in pregnancies where CF was diagnosed after fetal echogenic bowel detection (~65%). TOP and

caring for a child with CF were both associated with poor short-term parental psychological outcomes. Ethical analyses indicated that informed decisions should have been the main endpoint, rather than CF-affected births prevented.

Conclusion: CF testing leads to fewer CF-affected births. It is difficult to assess whether this means the test is valuable, since patients may not value TOP primarily in terms of maternal or fetal health outcomes, psychological or otherwise. The value of testing should arguably be measured in terms of improving patient autonomy rather than health.

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INTRODUCTION

Cystic fibrosis (CF) is caused by biallelic pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7.¹ CF is characterized by chronic bacterial airway and sinus infection, pancreatic exocrine insufficiency leading to incomplete breakdown of fats, congenital bilateral absence of the vas deferens (CBAVD) in males (leading to infertility), and a high sweat chloride concentration.² Progressive respiratory disease is the major cause of mortality and morbidity among young CF patients.

CF and other *CFTR*-related autosomal recessive disorders are usually found in people of Caucasian descent.³ The incidence of CF is greater than 1 in 2000 births in Scotland and Ireland, is approximately 1 in 3500 births in the United States, and is only 1 in 40,000–100,000 births in India.³ Almost 2000 different *CFTR* variants have been identified, though 85% of the disease burden is attributable to only a few variants.⁴ The most common pathogenic variant in the *CFTR* gene is a three-base pair deletion at position 508 resulting in the loss of phenylalanine (F508del). This variant accounts for ~70% of pathogenic *CFTR* variants globally, but the occurrence of F508del varies among different population

groups.¹ Most variants are either small or point deletions/insertions that are able to be detected by some panel-based *CFTR* tests, exon scanning-based *CFTR* genetic tests, and DNA sequencing.⁵

Prenatal testing and family cascade testing of pathogenic *CFTR* variants are expected to lower the incidence of CF over time as individuals are provided with information that may cause them to avoid pregnancy or terminate an affected pregnancy.³

In the case of prenatal *CFTR* testing, a fetus is typically only tested if it is considered to be at high risk of CF. This is the case when both parents are known carriers of at least one pathogenic *CFTR* variant, or when a fetal echogenic bowel (FEB) is detected during a second-trimester ultrasound. One study has estimated that 0.8–13.3% of fetuses with FEB will have CF.⁶ When both parents are carriers of pathogenic *CFTR* variants, there is a one-in-four chance (25%) of CF in the child, which is 625 times greater than the risk in the general population (0.04%).⁷ Prenatal *CFTR* testing is usually done through chorionic villus sampling or amniocentesis; however, clinical practice is currently shifting toward noninvasive prenatal testing for CF.^{8,9}

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The aim of this systematic review is to determine the effectiveness of prenatal genetic testing to diagnose pathogenic *CFTR* variants in pregnancies at high risk of CF. A key challenge in assessing a prenatal test lies in selecting appropriate endpoints to determine the clinical utility of the test. With this in mind, we also conduct a review of ethical considerations relating to genetic testing to support the interpretation of clinical findings. The ethics review synthesizes ethical arguments and analyses published in the literature. It is specific to genetic testing, and we apply its insights to prenatal testing for CF.

Earlier versions of the systematic review and ethics review were previously conducted by the authors in 2015 as part of a contracted assessment of the technology for the Australian Department of Health,¹⁰ to aid the Australian Government in making a policy decision regarding whether genetic testing for pathogenic variants in the *CFTR* gene ought to be publicly funded.¹⁰ This paper provides a more up-to-date systematic review and introduces additional discussion and considerations. Any opinions expressed belong to the authors or cited writers alone.

MATERIALS AND METHODS

Literature sources

Biomedical databases were searched from 1 January 1989 (the year the *CFTR* gene was identified) to 2015, updated on 26 February 2019, and included PubMed, Embase, the Cochrane Library, Web of Science, Current Contents, CINAHL, Scopus, and EconLit. Additional (gray) literature was sought (Supplementary Table S1). Search strategies used key text words and indexing terms (e.g., MeSH or EmTree) combined using Boolean logic (Supplementary Table S2).

Additional targeted searches were undertaken to determine the health implications of management changes, e.g., investigating the effects of termination of pregnancy (TOP) versus the effects of raising a child with CF. Key texts in medical ethics^{11,12} and web resources^{13–15} were sourced to help frame the ethics review (Supplementary Table S3).

Methodological approach

The clinical utility of a test is ideally determined by a trial of the test (direct evidence). Comparative studies that evaluate the outcomes of genetic testing and subsequent patient management versus patient management without genetic testing are needed as evidence of the effectiveness of the test. This type of evidence is rare.¹⁶ Where direct evidence is not available, a linked-evidence approach may be used to estimate the clinical utility of a test. This approach involves linking evidence from different parts of the test treatment pathway.¹⁷ The evidence must be transferrable between linkages, i.e., the patient population, setting, and test delivery should be the same across studies. We have systematically reviewed the evidence of the diagnostic performance of prenatal *CFTR* testing (with clinical diagnosis of CF as the reference standard), using the linked-evidence approach to determine whether testing would impact clinical management decisions.

We then considered whether this change in management would likely impact physical and psychological health outcomes. Evidence was systematically acquired and selected according to predetermined criteria for each step of the linked analysis (Supplementary Tables S4–S8). A review protocol was developed in consultation with an expert panel consisting of two clinical geneticists, a CF physician, and a senior genetic counselor. It is publicly available.¹⁸

Using clinically diagnosed CF as the reference standard is problematic, as this would be determined after birth. This was not possible where TOP was performed, and therefore false positive results may have been missed.

Study selection

The study selection process is outlined in Fig. 1.¹⁹ Twenty percent of titles and abstracts were screened for eligibility by two reviewers (S.J.M.K. and S.N.). Since this achieved good agreement, the remainder were screened by one reviewer (S.J.M.K.) per AMSTAR 2.²⁰ In cases of uncertainty regarding eligibility in the remainder, the second reviewer (S.N.) was consulted. Full-text articles were reviewed by S.J.M.K. The reference lists of potentially relevant studies were also searched.

Studies that met the prespecified criteria were eligible for inclusion (Supplementary Tables S4–S8). We excluded studies in languages other than English. The risk of bias in diagnostic performance studies was assessed using the QUADAS-2 tool.²¹ None of the included studies that assessed the impact of testing on management had a valid comparator, and this evidence was assessed using the Institute of Health Economics (IHE) appraisal checklist for case series.²²

Study profiles were developed that described the authors, publication year, study design, level of evidence, risk of bias, population characteristics, setting, study location, the test and other relevant interventions, length of follow-up, possible comparators, and relevant outcomes.

The broad literature search on test effectiveness also returned numerous articles discussing ethics of prenatal genetic testing. These studies were selected for the ethics review.^{23–27}

RESULTS

No direct evidence assessing the clinical utility of prenatal *CFTR* testing was identified.

Diagnostic performance of prenatal *CFTR* testing

Four studies investigated genetic *CFTR* testing in fetuses with two CF carrier parents. In these studies, biallelic variants in *CFTR* were detected in 8–22% of the fetuses, 38–58% were diagnosed as carriers, and 24–33% had no identifiable pathogenic variants^{28–31} (see Table 1). This roughly accords with the Mendelian inheritance pattern of a recessive trait (25% with the trait, 50% carrying the trait, 25% without the trait).

Two studies reported clinical outcomes after birth (the reference standard); no false negative test outcomes were

Fig. 1 Summary of the process used to identify and select studies for the systematic review.

recorded, i.e., there were no instances where children with CF were incorrectly identified as not having CF.^{29,30} However, neither the sensitivity nor specificity of testing could be determined, because carrier parents terminated pregnancies that were positive for biallelic pathogenic *CFTR* variants identified by prenatal tests.

Two studies investigated prenatal *CFTR* testing in pregnancies where FEB was detected. One study used denaturing gradient gel electrophoresis (DGGE) exon scanning of *CFTR* and DNA sequencing (see Table 1).³⁰ However, no clinical outcomes were reported because there was no clinical reference standard to compare prenatal test accuracy against. The majority (46/49; 94%) had no detectable pathogenic variants and the remaining 6% (3/49) only had one pathogenic variant identified and were considered carriers. No fetus was found to have biallelic pathogenic *CFTR* variants; possibly due to the small sample size and the relatively low CF rate in pregnancies with FEB (2–13%). The second study tested 25 fetal samples in pregnancies with detected FEB.³² One pathogenic variant was detected (CF carrier) and no CF diagnoses occurred before or after birth.

Five studies reported test failure rates of various panel-based *CFTR* tests, though not all of these tests were prenatal.^{33–37} The median failure rate between seven different tests was 4.5% (range 0.0001–9). This suggests that diagnostic

laboratories need to repeat ~4.5% of *CFTR* tests using panel-based tests. Test failures are usually resolved by sequencing the relevant amplicon or repeating the test.

No false positive results and very few false negative results were produced by pathogenic variant identification errors in a general population of patients suspected of CF (no prenatal testing). Amplification-refractory mutation system (ARMS) detection technology, used in two studies, produced the most identification errors due to the technology's inability to distinguish between homozygous and heterozygous states. In these studies, the second pathogenic variant could not be determined in the homozygous samples (5% of samples).^{38,39}

Misidentification errors were reported in two other noncomparative studies. In one study, 0.7% (7/1076) miscalls were made of the IVS8 5T/7T/9T polymorphism by a panel-based *CFTR* test using an oligonucleotide ligation assay.³⁶ Whereas, a second study reported that the panel-based *CFTR* test using fragment analysis and fluorescent polymerase chain reaction (PCR) used in their laboratory failed to detect a one base pair difference and was unable to recognize the F508C variant from wild type.³⁵

Change in management due to prenatal *CFTR* testing

Ten noncomparative studies reported the impact of prenatal *CFTR* testing on CF birth rates and TOP rates

Table 1 Diagnostic performance of *CFTR* testing in fetuses

Study country & risk of bias ^a	Population	Tests	Number of pathogenic variants detected	Fetus homozygous or compound heterozygous (has CF)	Fetus heterozygous (carrier)	Fetus has no pathogenic variants in <i>CFTR</i>	(Clinical) outcomes	Reference standard gaps
Kanavakis et al. ³⁰ , Greece, low risk of bias	N = 115 fetus samples from carrier parents	DGGE and PCR-mediated site-directed mutagenesis	Specific variant detection	22 (19%)	59 (51%)	34 (30%)	No false negatives; sensitivity = 100%	Fate of fetuses diagnosed with CF unknown
Kanavakis et al. ³⁰ , Greece, low risk of bias	N = 49 fetus samples in pregnancies with FEB detected by ultrasound	DGGE and DNA sequencing	All 27 exons and their exon–intron boundaries	0 (0%)	3 (6%)	46 (94%)	None were diagnosed with CF	No clinical outcomes reported
Collazo et al. ²⁹ , Cuba, low risk of bias	N = 72/108 fetus samples from couples with some risk of having a child affected by CF	ARMS and PCR-based restriction enzyme analysis	6	16 (22%)	27 (38%)	20 (28%)	Conclusive diagnosis was possible in 72/108 cases: 9 (12%) were either carrier or normal; no false negatives; sensitivity = 100%	Fate of fetuses diagnosed with CF unknown
Castaldo et al. ²⁸ , Italy, low risk of bias	N = 33 fetus samples from 32 high-risk couples (1 dizygotic twin pregnancy)	ASOH and STR genotyping	13 pathogenic variants and STRs	7 (21%)	18 (55%)	8 (24%)	All 7 CF fetuses were aborted	No clinical outcomes for carrier and normal fetuses reported
Miller et al. ³² , Canada, low risk of bias	N = 25 fetus samples in pregnancies with FEB detected by ultrasound	Panel of common <i>CFTR</i> pathogenic variants	50, including 23 variants recommended by the ACMG	0 (0%)	1 (4%)	24 (96%)	None were diagnosed with CF	No confirmed cases of CF after birth
Saker et al. ³¹ , France, some risk of bias	N = 12 fetus samples from carrier couples	PCR and STR genotyping	F508del and STRs	1 (8%)	7 (58%)	4 (33%)	Unknown	No clinical outcomes reported

ACMG American College of Medical Genetics and Genomics, ARMS amplification-refractory mutation system, ASOH allele-specific oligonucleotide hybridization, CF cystic fibrosis, DGGE denaturing gradient gel electrophoresis, FEB fetal echogenic bowel, PCR polymerase chain reaction, STR short tandem repeats.

^aBias was assessed using the QUADAS-2 tool for diagnostic accuracy studies.²²

Table 2 TOP and CF birth rate in pregnancies where an echogenic bowel is detected

Study	N tested/N total population (%)	N TOP/N CF positive diagnosed through prenatal testing (%) ^a	N CF positives diagnosed after birth	N children born with CF (%)
de Becdelièvre et al. ⁴¹	694/694 (100)	15/30 (50)	0 (although status remains unknown for 3 children)	15/694 (2.2)
Muller et al. ⁴³	641/641 (100)	16/18 (88.9)	2	4/641 (0.6)
Scotet et al. ⁴⁴	173/173 (100)	18/22 (81.8)	0	4/173 (2.3)
Slotnick & Abuhamad ⁴⁶	53/143 (37.6)	0/5 (0)	2	7/143 (4.9)
Ghose et al. ⁴²	48/60 (80)	1/1 (100)	2	2/60 (3.3)
Ameratunga et al. ⁴⁰	1/33 (3.0) (of 33 FEB pregnancies, there was only 1 carrier couple)	0/1 (0)	1	1/33 (3.0)

CF cystic fibrosis, FEB fetal echogenic bowel, PND prenatal diagnosis, TOP termination of pregnancy.
^a“CF positive” refers to a genetic diagnosis with biallelic pathogenic variants in *CFTR* (no clinical diagnosis)

Table 3 TOP and CF birth rate in pregnancies with a 1:4 risk of CF

Study	N tested/N total population (%)	N TOP/N CF positive diagnosed through prenatal testing (%) ^a	N CF positives diagnosed after birth	N children born with CF (%)
Scotet et al. ^{45b}	268/268 (100)	70/74 (94.6)	0	4/268 (1.5)
Scotet et al. ^{44b}	148/148 (100)	36/39 (92.3)	1	3/148 (2.0) + 1 fetus with CF lost
Tomaiuolo et al. ^{39c}	149/181 (82.3)	42/43 (97.7)	0	1/181 (0.6)
Castaldo et al. ^{28c}	33/33 (100)	7/7 (100)	0	0/33 (0)
Archibald et al. ⁴⁸	9/9 (100)	3/4 (75)	0	1/9 (11.1)

CF cystic fibrosis, PND prenatal diagnosis, TOP termination of pregnancy.
^a“CF positive” refers to a genetic diagnosis with biallelic pathogenic variants in *CFTR* (no clinical diagnosis).
^bPopulations of these studies are possibly overlapping.
^cPopulations of these studies are possibly overlapping.

(see Tables 2 and 3).^{28,40–48} Almost all studies were judged to be of high ($k = 5$) or moderate ($k = 4$) quality, with one study rated as low quality, per the IHE checklist (Supplementary Table S9).²² Six and five studies included pregnant women with detected FEB, and where a high risk (25%) of CF in offspring was identified, respectively (one study included both groups). In the absence of a comparator group, i.e., assessing pregnancy outcomes where *CFTR* testing did not occur, we assumed that without prenatal CF testing the pregnancies would not be terminated. We recorded pregnancies terminated after a CF-positive test result, i.e., two pathogenic variants detected in the fetus, as a “change in management” due to testing. Subsequently, the rate of births with CF and “CF births avoided” were calculated.

The rate of TOP after detecting biallelic pathogenic variants in *CFTR* is shown in Tables 2 and 3. Where both parents were CF carriers (1:4 chance of having a child with CF) and two pathogenic variants were identified in the fetus, the pregnancy was terminated in 75–100% cases (158/167 [94.6%] pregnancies). The TOP rate was slightly lower in pregnancies where CF was diagnosed prenatally after FEB was detected (and parents were not known carriers). TOP occurred in 50/77 (65%) of these cases. Overall, the TOP rate ranged from 0 to 100% (median 69.4%) across studies.

In these high-risk populations a relatively low number of children were born with CF, due to the high TOP rate. This shows there is a management change, i.e., TOP, after a positive prenatal genetic test result in most cases, assuming that pregnancies would continue (i.e., no TOP) in the absence of genetic testing.

The effect of change in management due to *CFTR* testing: parental psychological health after TOP compared with raising a child with CF

No controlled studies investigated the health impact from TOP after a prenatal CF diagnosis compared with the impact of no testing (and likely no TOP) and caring for a child with CF. Therefore, we conducted an indirect, narrative synthesis of the psychological impacts of TOP following prenatal testing for fetal abnormalities compared with no testing and caring for a child with CF.

In the population undergoing TOP, post-traumatic stress,^{49–56} grief,^{53,57–59} anger and guilt,⁵⁸ and depression^{50,52,54,59} were prevalent. Rates of grief (36–78%), post-traumatic stress (45.8–67%), and depression (~30%) were high in the first months after TOP, though these symptoms lessened over time. In these first few months post TOP, the rates of depression and anxiety were similar to those reported in studies among mothers of children with CF, with 48% and 20–34% of mothers scoring positive for anxiety and depression, respectively.⁶⁰ The evidence showed that psychological health improved over time in women who experienced TOP for fetal abnormality; however, evidence is lacking whether this is also the case for mothers of a child with CF. Severe anxiety and depression in parents of a child with CF was associated with younger age of the child.⁶⁰ However, another study reported that the age of affected

children correlated with caregiver burden: the higher the age, the greater the burden.⁶¹ Men showed fewer psychological symptoms than women, both in couples undergoing TOP and couples parenting a child with CF.⁶¹

Ethics review

Prenatal genetic testing raises ethical issues regarding the aim of testing, informed choice and counseling, the disability rights critique, privacy and confidentiality, and risks versus benefits.

Aim of prenatal genetic testing

Prenatal CF genetic testing cannot be used to prevent or blunt the development of disease for an individual. It can only serve to inform parents of the presence of fetal abnormality or disease, while any subsequent TOP prevents the birth of an individual who has the abnormality or disease.^{62–64} Controversial appeals have been made for the availability of prenatal testing to reduce societal spending on high-cost medical conditions.^{62,65} Opponents emphasize that using prenatal testing to reduce the prevalence of diseases like CF is morally problematic, because this promotes TOP as a means of reducing the number of people with particular medical conditions or needs. A perspective known as the disability rights critique emphasizes some respects in which widespread selective TOP would be morally problematic (see below). A general view has emerged that prenatal genetic testing should be regarded purely as a means of providing pregnant women and couples with information and thereby enhancing their capacity to make an informed choice, when they regard that information as relevant. This aim accords with the principle of respect for autonomy.

It is possible that TOP reduces suffering for the woman or couple. In this article, we considered this by assessing parental psychological health after TOP compared with raising a child with CF. However, it is philosophically contentious to propose that TOP reduces suffering for the child. This is because it is arguably nonsensical to speak of the suffering or experience of an individual who is never born on account of TOP. It is also implausible to suggest that to live a CF-affected life is worse than to have never been born. (To suggest this also sends a discriminatory message about CF patients, as we discuss below under the disability rights critique.) A woman or couple may opt for TOP, then later achieve a subsequent pregnancy and have a child unaffected by CF. This child's suffering has not been reduced, since this child is a different child (“nonidentical”) to the child whose birth was prevented by TOP. These matters are dealt with in philosophical discussion of the nonidentity problem.¹⁵

Informed choice and counseling

A person's choice is autonomous when they understand all of the relevant information and make the choice voluntarily, free of manipulation and coercion. Nondirective counseling is therefore crucial before and after testing. If information is patchy or biased, or if counseling is directive, then the aim of

providing information to enhance the capacity for autonomous choice is not met. Moreover, the aim effectively regresses to protecting society against the birth of children with often costly medical conditions through the use of selective TOP.⁶³

It is plausible that women and couples experience some initial pressure to opt for testing simply by virtue of the offer coming from medical professionals and institutions, since these are vested with considerable power and social standing.⁶⁵ This pressure potentially increases as the offer becomes more suggestive and as the opportunity to freely decline it becomes less clear, for instance through the routinization of testing.⁶⁵ Moreover, the patient may experience the mere lawfulness and availability of TOP following a positive test result as sources of pressure toward testing if the patient interprets these in terms of societal expectation. All of this reinforces the importance of nondirective counseling.

Most commonly women cite the following reasons for changing their mind about testing:

- “the level of risk ... for the condition in question” (in this case, CF)
- “the miscarriage risk of the test” (amniocentesis or chorionic villus sampling [CVS])
- “the method of termination which would be offered if they chose to terminate the pregnancy” following a positive test result.⁶²

It follows that these considerations are important to discuss during counseling, especially since women and health professionals tend to differ on what they regard as most important: women foremost value test safety, whereas health professionals foremost value test accuracy.⁶⁶

Disability rights critique

The disability rights critique opposes selective TOP as a means of preventing the birth of individuals with a particular medical condition or need. Prenatal testing arguably “sends the message that it would have been better if those living with the targeted conditions had not been born.”⁶⁴ Testing may therefore lead to increased discrimination within society, contrary to the principle of justice.⁴⁵ Some people are concerned that prenatal testing will “degrade society’s willingness to accept and care for” children deemed abnormal, while simultaneously narrowing the range of acceptable normality.⁶² Furthermore, some writers have argued that widespread acceptance of selective TOP would lessen efforts to develop cures for genetic disorders, though they have not provided evidence of this occurring.⁶²

Privacy and confidentiality

Genetic information is special in that genetic information about one individual can have implications for the lives of genetically related family members. For instance, if an individual opts against sharing their CF carrier status, this limits the ability of genetic relatives to make informed

reproductive choices. An ethical dilemma arises for the health professional when conflicted between maintaining confidentiality and informing genetic relatives of their risk. Instead of providing nondirective counseling, counselors may seek to persuade patients to share their CF carrier status or ask patients to allow them to share that information.¹¹ The potential benefits to genetic relatives could justify this. However, without authorization by the patient, disclosure by a health professional is ethically permissible (and may be required) only when the disclosure is both necessary and likely to succeed in lessening a serious threat to the health of a genetic relative, regardless of whether the threat is imminent.⁶⁷ The Institute of Medicine’s Committee on Assessing Genetic Risks has proposed that the following criteria must be met to justify a breach of confidentiality: (1) “all attempts to elicit voluntary disclosure, including intensive genetic counseling, must have failed”; (2) the seriousness and likelihood of the harm posed by the pathogenic variants must be clear; and (3) an effective preventive or therapeutic intervention must be available.²⁶ It is important to remember that there is only a risk for CF carriers and their genetic relatives if they are going to have children.

Prenatal testing can indicate nonpaternity.⁶⁸ Pretest counseling should discuss this possibility to ensure that the choice whether to undertake testing is informed. The doctor can inform the family of the genetic discrepancy and indicate that presumably this was a rare case of a *de novo* variant, if this was a possibility.⁶⁹ Unless the doctor has solid evidence, they have no right to suggest nonpaternity, since doing so could cause serious harm. If the doctor has solid evidence, then this should be shared with the patient if deemed relevant to medical decision making. Misinforming patients about test results would not be justified,⁶⁸ but a doctor could justifiably judge that the finding of nonpaternity was secondary, outside the primary purpose of the test, and therefore not disclose it.

Weighing up risks and benefits

The principles of beneficence and nonmaleficence imply that the benefits of a genetic test ought to outweigh, perhaps substantially, the risks of harm. It is important to consider “the predictive value of the test,” the benefits and harms of interventions associated both with the test (e.g., amniocentesis and CVS) and “with a positive test result” (e.g., TOP), and “the availability and acceptability” of those interventions.⁷⁰

DISCUSSION

The panel-based *CFTR* testing identified all variants that it is designed to detect.^{38,39} However, not every pathogenic *CFTR* variant is included in the panel, and a small percentage of patients with rarer variants would receive a false negative test result. Even if DNA sequencing were undertaken to try to detect these, around 2% would still be missed due to the inability to detect large deletions or insertions. Other methods such as multiplex ligation-dependent probe amplification (MLPA) would have to be conducted to identify these rarer

variants. Moreover, the panel-based test failure rate was around 4.5%, so some tests would need to be repeated to get a valid result. It is important to explain to patients the likelihood of the fetus being truly negative in view of these limitations of the panel-based test.

Evidence indicating a change in patient management (e.g., TOP) following prenatal *CFTR* testing was found, although the data were noncomparative. TOP rates in pregnancies determined to be CF-positive after FEB detection varied widely (0–100%; Table 2). Heterogeneity among studies was expected in view of religious and cultural variation regarding the acceptability of TOP. However, all included studies were conducted in Europe, the UK, the United States, and Australia, which share religious and cultural histories. TOP is legal in these countries, with varying restrictions, though access to quality health care and TOP may vary. The most straightforward explanation of the difference in TOP rates may simply relate to chance, in connection with the very small sample size. The number of test positives was very low ($n = 1$ and $n = 5$) in studies with a 0% TOP rate. Furthermore, in the case of carrier couples, *CFTR* testing is usually done at a lower gestational age, compared with testing undertaken due to a second-trimester FEB detection. This means that carrier couples can opt for TOP at an earlier time point. This could explain why the TOP rate was higher in carrier couples (around 95% after a positive prenatal genetic test result) compared with FEB pregnancies (around 65% after a positive prenatal genetic test result). We did not have access to individual patient data and therefore were unable to conduct analyses adjusting for gestational age.

In our analysis of psychological outcomes, we found that short-term anxiety and depression rates were similar between women who underwent TOP due to fetal abnormality and women who had a child with CF (although evidence was noncomparative). Less is known about the long-term effects and other potential health impacts. Grief, post-traumatic stress, anger, depression, and guilt were prevalent after TOP. However, this decreased slowly over time. Similar rates of depression and anxiety were also prevalent among mothers of children with CF, with the rate of depression being associated with the younger age of the child, though caregiver burden increases with the age of the child. One study reported that only 8% and 10% of women who underwent TOP later reported feelings of regret and doubt respectively, suggesting that most women who opted for TOP valued having the option.⁵⁴ It should be noted that the psychological health of parents of a child with CF may not be directly comparable with the psychological health of parents who underwent TOP for fetal abnormality, since fetal abnormalities include disorders that are substantially more severe than CF.

There are concerns that prenatal testing may degrade society's willingness to accept and care for children with CF. This is one important reason why the success of testing ought not to be gauged in terms of the number of CF births

prevented. Prenatal testing for fetal abnormalities should instead serve the aim of providing pregnant women and couples with information to enhance their autonomy. Nondirective counseling is crucial both for ensuring informed and voluntary consent to testing and for retaining the test's aim of simply informing, rather than directing, reproductive choices. The exception to this is when the woman or couple should be counseled toward sharing information with family members who may attach significance to it when making their own reproductive decisions.

It is important not to confuse informing a choice with improving health, since a more informed choice may not lead to improved health. However, to assess the effectiveness of a health technology is to assess the benefit or value of the technology.⁷¹ While this typically lies in improving health, there are some exceptions, where the benefit or value lies elsewhere. For example, in vitro fertilization arguably does not improve health but instead overcomes the problem of childlessness. Our review of ethical considerations reveals persuasive reasons for regarding prenatal genetic testing for CF as a case where the benefit of the technology lies not in improving health, but in informing reproductive choice. In this way, our review suggests that test effectiveness ought to be assessed in terms of enhancing autonomy. Emerging technologies that can be used after birth to improve health outcomes for some CF patients, such as ivacaftor, may “influence the decision-making process of parents who receive a fetal diagnosis of CF,” leading to less TOP.⁷² This does not alter the effectiveness of *CFTR* testing if that is assessed in terms of enhancing autonomy rather than in terms of reducing the CF birth rate. By contrast, if technologies emerge that can be used antenatally to improve health outcomes for some CF-affected fetuses, then a codependent assessment of the effectiveness of *CFTR* testing may be warranted as part of new clinical pathways, including antenatal treatments, to prevent or slow the development of disease in affected individuals.

The ethics review also has implications for assessing the cost-effectiveness of *CFTR* testing, favoring as the primary endpoint something like cost per informed choice rather than cost per CF birth averted. One could measure the cost-effectiveness of CF testing followed by TOP in terms of health benefits for the parents. However, as we have shown, the evidence suggests that parental psychological health after TOP, compared with raising a child with CF, may be comparable, so there may be no clear health benefit for the parent. Meanwhile, one cannot measure the cost-effectiveness of CF testing followed by TOP in terms of health benefits for the fetus or child, since there are philosophical problems with describing TOP as beneficial for the fetus or any subsequent child.

This review was limited by the nonsystematic search of the ethics literature. Furthermore, we relied on a linked-evidence approach due to the absence of direct evidence. Psychological impact evidence was noncomparative and was therefore discussed as a naïve indirect comparison.

CONCLUSION

CFTR testing does influence patient management, very often leading to TOP when the test result is positive. Psychological outcomes for women undertaking TOP may be similar to psychological outcomes for women having a child with CF, at least in the short term, so the health impact of the test may be minimal in this respect. Two points are important to make.

First, the evidence is limited; the psychological impact of prenatal testing, and any subsequent decisions, requires further research. This may allow more value to be placed on the test. Change in management following a positive test result could also take the form of professional counseling in preparation for raising a child with CF, and the value of this should be assessable in terms of improved psychological outcomes for parents.

Second, the value of the test is difficult to assess because the value of TOP to women and couples opting for it may not be reducible to health outcomes, psychological or otherwise. It could be argued that CFTR testing ought to be valued in terms of enhancing patient autonomy rather than improving health.

SUPPLEMENTARY INFORMATION

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DISCLOSURE

The authors declare no conflicts of interest.

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