NACFC, regional CF conferences, and online. Current projects include dissemination of educational resources and guideline implementation toolkits using Dropbox; development of training materials on CF for community mental health providers; and facilitation of CBT peer study groups for mental health coordinators and other CF team members, including educational consultation with a CBT expert.

Consultation and Guidance. The Consultation and Guidance workgroup will be responsible for supporting, partnering and consulting with care centers during guideline implementation. This group will serve as a point of contact for care centers to address specific questions regarding the logistics of screening, assessment and intervention; coordinate with local CF Foundation chapter executive directors; and connect with additional committees and workgroups within the National CF Foundation for mental health inclusion. Current projects include development of the mental health coordinator listserv; facilitating mental health first aid training and certification at Compass; adding standardized mental health questions to the "Co-Production of Care" Dashboard; and providing guidance regarding licensure and third-party insurance billing.

Research. The Research workgroup will be responsible for identifying and promoting research initiatives that: 1) increase our understanding of the prevalence of depression and anxiety in individuals with CF and parent caregivers (in relation to age, gender, and disease severity), 2) identify risk factors and triggers for developing symptoms of psychological distress, 3) quantify the effects of these symptoms on health outcomes and quality of life, and 4) evaluate the training and education needs of the newly funded Mental Health Coordinators, and their effectiveness in implementing the screening guidelines and referral processes. To address these questions, one of our central goals will be inclusion of annual screening scores from the PHQ-9 and GAD-7 into the CF Foundation Registry. We also plan to develop templates for integrating screening scores into existing electronic medical records, such as EPIC, which would document scores as well as notes on any necessary follow-up clinical assessment, referral or intervention. Depression and anxiety scores from the TIDES study at 45 US CF centers will also be utilized to provide initial answers to the questions listed above, facilitating future CFF Registry studies using the PHQ-9 and GAD-7.

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S12.1
MOUSE MODELS EXPRESSING HUMAN CFTR TO TEST CFTR-DIRECTED THERAPIES

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Until recently, the vast majority of treatments for cystic fibrosis (CF) have focused on treating the symptoms of the disease, not the source. After the identification of the *CFTR* gene in 1989, the idea of correcting the basic genetic defect of CF through CFTR-directed therapies could be realized. Today there are multiple CFTR-directed therapies that are FDA approved or are being evaluated for their feasibility and effectiveness in restoring CFTR function.[1-3] These therapies include gene therapy as well as CFTR modulation through molecules that allow for CFTR correction, potentiation or even readthrough of premature termination codons. Some of these therapies are directed toward specific CFTR mutation classes while others may be relevant to all CFTR mutations. Whether it be these therapies or ones that do not yet exist, the CF research community needs novel and innovative in vivo tools to test the practicality and efficacy of these CFTR-directed therapies. While cell lines expressing exogenous mutant CFTR have been critical in identifying beneficial drugs through high-throughput screens, their predictive value for clinical benefit in CF patients can still be questioned. Animal models allow for in vivo testing of CF treatments but animal and human *CFTR* sequence and gating differences are concerning with respect to specific CFTR-directed therapies.[4,5] Without in vivo expression of human *CFTR* containing CF disease-causing mutations, a true clinical prediction of CFTR-directed therapies effects in patients may not be achieved. We are creating such a model by combining the many benefits of a mouse model with the ability to express human *CFTR* containing common *CFTR* mutations under the control of its adjacent endogenous regulatory elements.

The human *CFTR*-expressing mouse (h*CFTR*) was created by the insertion of a ~260 kb bacterial artificial chromosome (BAC) containing 40 kb of sequence 5' of the transcriptional start site, the human *CFTR* gene of 189 kb and 25 kb 3' to the end of *CFTR*.[6] One founder mouse with strong human *CFTR* expression was bred to establish the h*CFTR* colony. The BAC inserted into a single integration site on mouse chromosome 8. Human CFTR expression was detected in various tissues in the mice from this strain. To verify that h*CFTR* expression could complement the loss of mouse CFTR (m*CFTR*), the h*CFTR* expressing strain was crossed to a strain carrying a m*Cftr* null mutation.[7] Subsequently, h*CFTR* positive(+) CF mice were compared to h*CFTR* negative(-) CF littermates. hCFTR+ CF mice displayed robust CFTR function in the airway compared to h*CFTR*- CF mice (nasal potential difference: -8.43 ± 2.4 mV vs 1 ± 0.6, respectively) as well as in the intestine (small intestinal short-circuit current (Isc) response to forskolin/IBMX: -87.5 ± 8.8 $\mu A/cm^2$ vs -5.6 ± 2.1 $\mu A/cm^2$, respectively) and evidence of bicarbonate permeability (forskolin Cl^- free Isc: -37.6 ± 7.4 vs -8.4 ± 3.0 $\mu A/cm^2$). hCFTR+ CF mice displayed normal survival, intestinal histology, and growth while h*CFTR*- CF mice displayed reduced survival due to intestinal obstruction, mucus anchoring to goblet cells, abnormal intestinal histology and reduced growth. These data suggest that h*CFTR* complements the loss of m*Cftr* and can be utilized to create specific human *CFTR* mutations for examining the efficacy of CFTR-directed therapies.

We are currently creating five human CFTR mutations (F508del, G542X, W1282X, G551D and 3849+10kb C>T) in the h*CFTR* mouse strain that will allow various CFTR-directed therapies to be tested. To introduce these desired *CFTR* mutations in a quick and efficient manner, we are utilizing the genome editing system CRISPR/Cas9.[8] We have successfully created several m*Cftr* mutations using CRISPR/Cas9 already. Single guide RNAs (sgRNAs) that are used in this system to direct the nuclease to the correct DNA sequence have been designed and validated in vitro for all five of the desired *CFTR* mutations. Optimal sgRNAs, Cas9 nuclease and oligonucleotides carrying the desired *CFTR* mutation are being injected into one-cell mouse embryos from the C57Bl/6J background and implanted in pseudo-pregnant mice by the CWRU Transgenic and Targeting Facility. DNA from the resulting pups of these five lines will be sequenced using next generation sequencing with a MiSeq instrument allowing for the accurate identification of mutations present. Once each desired *CFTR* mutation is identified in founder mice, they will be crossed to a m*Cftr* null strain and characterized for loss of CFTR function. The successful creation of these h*CFTR* mutation carrying strains will allow for the in vivo evaluation of various CFTR-directed therapies which may directly impact the lives of CF patients.

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S12.2
RABBIT MODELS FOR CYSTIC FIBROSIS

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Cystic fibrosis (CF) animal models have contributed significantly to uncover the underlying mechanisms of the disease. However, existing CF animal models have their limitations, either because the animal models fail