and examine the association between sociodemographic characteristics and sources of communication, adjusting for clinical and health belief factors as covariates. RESULTS/ANTICIPATED RESULTS: This study is in progress. It is anticipated that the most overall prevalent method of communication about genetic testing will be via the media. In multivariate models, it is anticipated that women who are younger, Black, have a lower education, have lower income, and no health insurance are more likely to receive communication about genetic testing from a source other than a health professional or not at all. After adjusting for clinical and health belief factors such as co-morbid conditions, having a primary care physician, and general knowledge about genetic testing, there may be some association between the above mentioned sociodemographic factors and receiving communication about genetic testing via a healthcare professional. DISCUSSION/SIGNIFICANCE: Reporting on the association between sociodemographic factors and sources of communication can aid in an intervention design to better promote genetic testing. This can be most beneficial among vulnerable groups like Black women to better understand their own genetic risk of cancer and to make informed decisions about their health.

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The impact of asymmetric lung injury on gas and pressures distribution in a mechanical ventilation model with implementation of compartmentalized inspiratory hold*

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OBJECTIVES/GOALS: Asymmetries in lung pathophysiology can result in a maldistribution of gas between regions of the lungs which may generate dangerous pressures that are not observable by clinicians. Our study aims to demonstrate and quantify this through use of high-fidelity simulators to represent a range of commonly encountered clinical pathologies. METHODS/STUDY POPULATION: A benchtop study was performed with two high-fidelity breathing simulators, each representing one lung. This system allows for real-time monitoring of pressure and lung dynamics in a two-lung asymmetric injury model. One simulator was set to a fixed compliance and a resistance. A second simulator had a range of compliance and resistance values. Data were collected for 15 different test cases across a distribution of asymmetries. Each test case is run for 30 cycles. At the end of each ventilatory cycle, a short expiratory hold is performed, allowing pressure in the lung simulator, tubing, and ventilator circuit to equilibrate between cycles. RESULTS/ANTICIPATED RESULTS: Maldistribution of tidal volume was demonstrated when the compliance ratio between lung models (CL1/CL2) was 0.2 and the resistance ratio (RL1/RL2) was 10 with 23.9% (99% CI: 23.9-24.0%) of the gas volume distributed to lung 1 (103 mL L1 vs 327 mL in L2). Additionally, the injured lung when compared with the normal lung experienced higher peak pressures (12.8 cm H2O vs. 6.9 cm H2O, L1 and L2 respectively) and higher compartmentalized plateau pressures (11.5 cm H2O vs. 6.8 cm H2O, L1 and L2 respectively). DISCUSSION/SIGNIFICANCE: We demonstrate significant maldistribution of volume and pressures between two lungs in an asymmetric injury model. This study suggests significant impact of asymmetry in current lung-protective mechanical ventilation strategies and calls for better understanding of case-specific pathophysiologic changes affecting each of the two lungs.

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Developing a Digitally Integrated Endotracheal Tube for Neonates to Improve Safety and Respiratory Function

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OBJECTIVES/GOALS: Neonatal endotracheal tubes (ETTs) are usually uncuffed to avoid subglottic stenosis and other complications, but cuffed ETTs allow better ventilation. Our goal was to detect and control pressure in the cuff below the limit of occluding venous flow to minimize the risk of subglottic stenosis. METHODS/STUDY POPULATION: We designed a pressure sensor to fit on a 2.5 ETT for prototype testing in 8 age adult female rabbits. Eight uncuffed age- and sex- matched rabbits served as control. Study duration was 2 hours during which pressure in the cuff was limited by novel sensor (intervention) or auscultation (control). Anesthesia was maintained with sevoflurane. Ventilation was provided mechanically. Subsequently the tracheae were removed, sectioned crosswise, and compared histologically for mucosal damage. RESULTS/ANTICIPATED RESULTS: Preliminary data demonstrated an almost 30% greater amount of intact mucosa in the intervention group. The sensor also provided data on heart rate and respiratory rate, although this signal was not optimal. After filing an invention disclosure and provisional patent, we are refining our device to include multiple compartments for local control of cuff pressure and applying for a STTR Phase I/II application. DISCUSSION/SIGNIFICANCE: Ventilation in neonates with uncuffed ETTs can be suboptimal due to leak around the tube, but cuffed ETTs pose the threat of subglottic stenosis and other complications. We have designed a prototype cuffed ETT with a sensor to maintain low cuff pressure while preventing leaks and largely avoiding damage to the tracheal mucosa.

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Decreased Contraction Rate, Altered Calcium Transients, and Increased Proliferation seen in Patient-specific iPSC-CMs Modeling Ebsteins Anomaly and Left Ventricular Noncompaction

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OBJECTIVES/GOALS: In a familial case where 10 of 17 members inherited EA/LVNC in an autosomal dominant pattern, we discovered a novel, damaging missense variant in the gene KLHL26 that segregates with disease and comprises an altered electrostatic surface profile, likely decoupling the CUL3-interactome. We hypothesize that this KLHL26 variant is etiologic of EA/LVNC. METHODS/

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STUDY POPULATION: We differentiated a family trio (a heart-healthy daughter and EA/LVNC-affected mother and daughter) of induced pluripotent stem cells into cardiomyocytes (iPSC-CMs) in a blinded manner on three iPSC clones per subject. Using flow cytometry, immunofluorescence, and biomechanical, electrophysiological, and automated contraction methods, we investigated iPSC-CM differentiation efficiency between D10-20, contractility analysis and cell cycle regulation at D20, and sarcomere organization at D60. We further conducted differential analyses following label-free protein and RNA-Seq quantification at D20. Via CRISPR-Cas9 gene editing, we plan to characterize KLHL26 variant-specific iPSC-CM alterations and connect findings to discoveries from patient-specific studies. RESULTS/ANTICIPATED RESULTS: All iPSC lines differentiated into CMs with an increased percentage of cTnT+ cells in the affected daughter line. In comparison to the unaffected, affected iPSC-CMs had fewer contractions per minute and altered calcium transients, mainly a higher amount of total calcium release, faster rate of rise and faster rate of fall. The affected daughter line further had shorter shortening and relaxation times, higher proliferation, lower apoptosis, and a smaller cell surface area per cardiac nucleus. The affected mother line trended in a similar direction to the affected daughter line. There were no gross differences in sarcomere organization between the lines. We also discovered differential expression of candidate proteins such as kinase VRK1 and collagen COL5A1 from proteomic profiling. DISCUSSION/SIGNIFICANCE: These discoveries suggest that EA/LVNC characteristics or pathogenesis may result from decreased contractile ability, altered calcium transients, and cell cycle dysregulation. Through the KLHL26 variant correction and introduction in the daughter lines, we will build upon this understanding to inform exploration of critical clinical targets.

Regulatory Science

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Youth Nicotine Addiction: Strategic Defiance of Regulatory Oversight by the Disposable Electronic Nicotine Delivery System Industry

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OBJECTIVES/GOALS: To assess the impact of federal regulations and policies relating to disposable Electronic Nicotine Delivery Systems (ENDS) on youth consumption of these products by identifying factors enabling its growing consumption among youth users and its relation to adolescent addiction to nicotine. METHODS/STUDY POPULATION: Disposable ENDS are all-in-one devices with pre-filled nicotine liquid and a built-in battery. Recent data shows increased sales as users, including youth, are switching from pod-based to disposable ENDS. Thus, an understanding of the regulatory landscape for these products will provide insight on how to mitigate youth nicotine addiction. Data from the Centers for Disease Control and Prevention 2021 National Youth Tobacco Survey (NYTS) was analyzed for patterns of adolescent use. FDA statements and actions involving disposable ENDS companies were reviewed to evaluate the current FDA stance. Analyses of both data sets identified factors enabling the growth in sale of disposable ENDS. RESULTS/ANTICIPATED RESULTS: The NYTS reported 53.7% of youth ENDS users report using disposable ENDS and Puff Bar is the leading ENDS device among youth consumers. In March 2021, Puff Bar announced a return to market with "tobacco-free nicotine" after ceasing sales following an FDA warning letter in July 2020. But synthetic nicotine retains the same chemical properties as tobacco-derived nicotine and the same risks for addiction and abuse. The Food and Drug Administration (FDA) maintains synthetic nicotine products will be regulated on a case-to-case basis, suggesting "closed system devices" containing synthetic nicotine may not be regulated as tobacco products. DISCUSSION/SIGNIFICANCE: The growing popularity of disposable ENDS among youth is problematic. Awareness of strategic regulatory defiance (i.e., Puff Bar), will bring light to industry sales tactics. To develop comprehensive data on disposable ENDS use by young adults, an anonymous survey of college students will be conducted.

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Therapeutic Class Labeling of EGFR Companion Diagnostics (CDxs)

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OBJECTIVES/GOALS: Review all approved companion diagnostics (CDxs) labeling for therapeutic class language. Examine the regulatory pathways of CDx products whose labels contain therapeutic class labeling. Develop recommendations for pharmaceutical industry professionals on best practices in the co-development of CDxs and oncology therapeutic products. METHODS/STUDY POPULATION: Literature discussing companion diagnostics was reviewed from EBSCOhost, PubMed, and OVID. The Intended Use language within CDx labels on the Food and Drug Administrations "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website were reviewed on November 1, 2021 for therapeutics class language. For CDx products with therapeutic class label language, the regulatory history was evaluated to determine the development approach taken to achieve the language. RESULTS/ANTICIPATED RESULTS: A total of 45 CDxs were identified, of which only 2 contained therapeutic class labeling, both of which were devices for the identification of epidermal growth factor receptor (EGFR) mutations for the treatment of non-small cell lung cancer (NSCLC). Three additional EGFR CDxs were approved; however, they did not contain therapeutic class labeling. The first CDx was the Cobas EGFR Mutation Test V2, which received therapeutic group label language as an update on October 27, 2020; however, prior to the therapeutic class labeling, three oncology products were named in the Intended Use: Tarceva (erlotinib), Tagrisso (osimertinib), and Iressa (gefitinib). The second CDx to incorporate therapeutic class labeling was the ONCO/Reveal Diagnostic Lung and Colon Cancer Assay upon initial approval on July 30, 2021. DISCUSSION/SIGNIFICANCE: EGFR CDxs are the first to shift towards therapeutic class labeling. Indication, molecular alterations, and mechanism of action of the approved therapeutic class products, number of products approved, as well as CDx analytical and clinical validation influence class label relevance. Discussions with the FDA are encouraged early in development.

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