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(54) Title: ANTI-ANDROGEN OR AN ANDROGEN RECEPTOR ANTAGONIST FOR TREATMENT OF A VIRAL RESPIRATORY INFECTION

(57) Abstract: The present disclosure includes methods, systems, kits and compositions for treating, preventing and diagnosing viral infections, specifically SARS-CoV-2 infections, with an anti-androgen and anti-thyroid medication, a thyroid receptor antagonist, a TGF- $\beta$  inhibitor or a combination thereof. The present disclosure also describes methods and compositions for the treatment of viral respiratory diseases, specifically SARS-CoV-2 infections, including anti-androgens, anti-thyroid medications, thyroid receptor antagonists, TGF- $\beta$  inhibitors, RXR inhibitors, furin inhibitors or other agents to disrupt the androgen signaling.



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ANTI-ANDROGEN OR AN ANDROGEN RECEPTOR ANTAGONIST FOR TREATMENT  
OF A VIRAL RESPIRATORY INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** The international application is related to and claims the benefit of U.S. Utility Application No. 16/946,875, titled Systems, Methods, and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on July 9, 2020, which is a continuation in part application to U.S. Utility Application No. 15/929,788, titled Systems, Methods, and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 21, 2020, which is related to and claims the benefit of U.S. Provisional Application No. 63/001,629, titled Systems, Methods and Kits for Diagnostics and Treatment of SARS-CoV-2, filed on March 30, 2020, U.S. Provisional Application No. 63/004,171, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on April 02, 2020, U.S. Provisional Application No. 63/004,398, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on April 02, 2020, U.S. Provisional Application No. 62/704,126, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on April 22, 2020, U.S. Provisional Application No. 62/704,416, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 08, 2020, U.S. Provisional Application No. 62/704,531, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 14, 2020, and U.S. Provisional Application No. 63/041,426, titled Methods and Compositions for the Treatment of Viral Respiratory

Infection, filed on June 19, 2020, the entire contents of each being incorporated herein by reference.

## FIELD

[0002] The present invention relates to systems, methods, compositions and kits for treating, preventing, and diagnosing viral infection using a combination of thyroid hormone pathways and androgen mediated pathway. The present invention relates to methods and kits for predicting viral respiratory disease severity. Additionally, the present invention relates to methods and kits for guiding treatment of viral respiratory disease by testing for polymorphisms in the androgen receptor gene or genes under regulatory control of the androgen receptor. Similarly, the following invention relates to systems and methods for treatment of viral respiratory diseases with various anti-androgens used in combination with thyroid inhibitors including, but not limited to, androgen receptor antagonists, androgen synthesis inhibitors, or antigonadotropins used in combination with TGF- $\beta$  inhibitors, thyroid hormone receptor inhibitors, thyroid inhibitors, or furin protease inhibitors. Additionally, the present systems, methods, and kits are useful for treating, preventing, and diagnosing coronavirus, e.g., SARS-CoV-2 (COVID-19).

## BACKGROUND

[0003] In late 2019, a novel coronavirus, subsequently named SARS-CoV-2 (COVID-19), was first reported in Hubei province in China. Since it was first reported, a worldwide pandemic has ensued affecting more than 450,000 individuals as of March 2020. In the midst of the pandemic, epidemiological reports unveiled a disproportionate low rate of severe cases among adult females compared to adult males, 42% and 58%, respectively.

Similarly, the rate of severe cases among pre-pubescent children was exceptionally low at 0.6% (*See Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020*). An explanation for the skewed prevalence of severe COVID-19 infection in adult males has yet to be elucidated.

**[0004]** In newborns, it has long been recognized that male infants are more susceptible to respiratory distress syndrome (*See Torday JS, Nielsen HC, Fencel Mde M, Avery ME. Sex differences in fetal lung maturation. Am Rev Respir Dis. 1981; 123(2): 205-208*) and less likely to respond to prenatal glucocorticoid therapy to protect against respiratory distress. Respiratory distress is intimately tied to the production of pulmonary surfactant, e.g., pulmonary surfactant proteins have been demonstrated to protect against influenza A (*See Hartshorn KL, Crouch EC, White MR, Eggleton P, Tauber AI, Chang D, Sastry K. Evidence for a Protective Role of Pulmonary Surfactant Protein D (SP-D) Against Influenza A Viruses. J Clin Invest. 1994; 94 (1): 311-319*). In animal studies, it was demonstrated that a sexual dimorphism in fetal pulmonary surfactant production is influenced by the androgen receptor (AR) (*See Nielsen HC. Androgen receptors influence the production of pulmonary surfactant in the testicular feminization mouse fetus. J Clin Invest. 1985; 76(1): 177-181*). For example, in rabbits, dihydrotestosterone was shown to inhibit fetal pulmonary surfactant production in both males and females while an anti-androgen, flutamide, was demonstrated to remove the sexual dimorphism in surfactant production.

**[0005]** While severe COVID-19 symptoms are primarily manifested in older adults, the similar sexual dimorphism in the severity of respiratory disease is of interest. In addition, AR expression is low prior to pubertal maturation and may contribute to the low incidence of

severe COVID-19 infection in children. The lower rate of severe COVID-19 infection in female patients may be attributed to lower androgen receptor expression.

#### SUMMARY

[0006] SARS-CoV-2 is part of the coronavirus family of viruses including SARS-CoV-1 and MERS-CoV. Coronavirus predominantly infects type II pneumocytes in the human lung (*See* Shieh WJ, Hsiao CH, Paddock CD, Guarner J, Goldsmith CS, et al. Immunohistochemical, in situ hybridization, and ultrastructural localization of SARS-associated coronavirus in lung of a fatal case of severe acute respiratory syndrome in Taiwan. *Hum Pathol.* 2005; 36(3): 303-309). It has been demonstrated that SARS-CoV-2 cell entry depends on priming of a viral spike surface protein by transmembrane protease serine 2 (TMPRSS2) present in the host. In type II pneumocytes, TMPRSS2 expression is associated with an increase in androgen receptor (AR) expression (*See* Mikkonen L, Pihlajamaa P, Sahu B, Zhang FP, Jänne OA. Androgen Receptor and Androgen-Dependent Gene Expression in Lung. *Mol Cell Endocrinol.* 2010; 317 (1-2): 14-24), specifically connecting AR expression to SARSCoV-2, due to AR-regulated TMPRSS2 gene promoter (*See* Lin B, Ferguson C, White JT, Wang S, Vessella R, True LD, et al. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. *Cancer Res* 1999; 59: 4180–4). Moreover, angiotensin converting enzyme 2 (ACE2) has been recognized as the attachment molecule to the viral spike surface protein, thus termed the “receptor of SARS-CoV-2” (*See* Y. Qiu, Y.-B. Zhao, Q. Wang, J.-Y. Li, Z.-J. Zhou, C.-H. Liao, X.-Y. Ge, Predicting the angiotensin converting enzyme 2 (ACE2) utilizing capability as the

receptor of SARS-CoV-2, *Microbes and Infection*, <https://doi.org/10.1016/j.micinf.2020.03.003>).

**[0007]** Additionally, SARS-CoV-2 spike protein has been revealed to contain a furin cleavage sequence (*See* Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. *Infez Med.* 2020; 28(2): 174-184). As such, viral spike protein priming may be mediated through furin protease in addition to TMPRSS2. Furin expression has been demonstrated to be up-regulated by thyroid hormone T<sub>3</sub> and its expression was cooperative with transforming growth factor beta or TGF-β (*See* Chen RN, Huang YH, Lin YC, et al. Thyroid hormone promotes cell invasion through activation of furin expression in human hepatoma cell lines. *Endocrinology.* 2008; 149(8): 3817-3831. doi:10.1210/en.2007-0989). Thyroid hormone T<sub>3</sub> or T<sub>4</sub> binds to thyroid hormone receptor (TR), which then activates genes containing thyroid hormone response elements (TREs) in the regulatory regions of target genes. As such, a furin protease inhibitor, a modulator of T<sub>3</sub>, a modulator of T<sub>4</sub>, a TR inhibitor, or a TGF-β inhibitor (TGF-βi) are envisioned to be used in combination with an anti-androgen to limit the expression of TMPRSS2 and furin.

**[0008]** Males infected with SARS-CoV-2 are more likely to be admitted to the ICU compared to females. Various theories have been put forward to explain this disparity. Previously, we have reported that among hospitalized COVID-19 patients, 79% presented with male pattern baldness compared to 31-53% that would be expected in a similar aged match population. Male pattern baldness is known to be mediated by variations in the Androgen Receptor (AR) gene. In addition, the only known promoter of the enzyme

implicated in SARS-CoV-2 infectivity is an androgen response element. The polyglutamine repeat (CAG repeat) located in the first exon of the AR gene is associated with androgen sensitivity, testicular cancer and androgenetic alopecia. These observations led us to hypothesize that variations in the AR gene may pre-dispose male COVID-19 patients to increased disease severity; therefore, we conducted a prospective longitudinal study of hospitalized COVID-19 male patients. ICU admission rates for patients with a short (<22) CAG repeat were compared to ICU admission rates for patients with a long ( $\geq 22$ ) CAG repeats. Consistent with our hypothesis, 45% of patients with a short CAG repeat were admitted to the ICU compared to 70% of patients with a long CAG repeat ( $p=0.0429$ ). Compared to hospitalized COVID-19 male patients with a short CAG repeat, hospitalized COVID-19 male patients with a long CAG repeat had a significantly increased risk for admissions to ICU (RR 1.5630 , 95% CI: 1.0022 to 2.4378 ,  $p=0.0489$  ). Further, the average duration of hospitalization for patients with a long CAG repeat was 37 (+/-21) days compared to 27 (+/- 20) days for patients with a short CAG repeat. We believe this is the first study to demonstrate a direct association between androgen receptor genetic variants and COVID-19 disease severity. If the results of our study are replicated in a larger cohort, genetic testing could potentially help identify patients at increased risk for COVID-19 disease severity.

**[0009]** Additionally, TR regulates gene expression by binding to TREs in DNA either as monomers, heterodimers with other nuclear receptors. One important nuclear receptor that TR forms dimers with is the retinoid X receptor (RXR), a nuclear retinoic acid receptor. TR/RXR heterodimers are the most transcriptionally active form of TR. As such inhibition of RXR would inhibit TR activity.

[0010] The present invention relates to systems, methods, compositions and for diagnosing and treating a viral respiratory infection which may include first measuring polymorphisms in the androgen receptor gene or polymorphisms in genes under regulatory control of the androgen receptor. Identification of polymorphisms in the androgen receptor gene can be used to guide treatments of viral respiratory diseases or infections. Treatments for viral respiratory diseases may include, but are not limited to, androgen receptor antagonists, androgen synthesis inhibitors, or antigonadotropins used in combination with TGF- $\beta$  inhibitors, thyroid hormone receptor inhibitors, thyroid inhibitors, or furin protease inhibitors. Specifically, the present systems, methods, compositions and kits are useful for treating, preventing, and diagnosing viral respiratory disease as a result of coronavirus infection, e.g., SARS-CoV-2 (COVID-19).

#### DETAILED DESCRIPTION

[0011] As used herein, the terms “prevent” or “prevention” and other derivatives of the words, when used in reference to viral respiratory infection, e.g., viral respiratory infection, refer to a reduced likelihood of viral respiratory infection in an individual receiving a given treatment relative to that of a similar individual at risk for viral respiratory infection but not receiving that treatment. As such, the terms “prevent” and “prevention” encompass a treatment that results in a lesser degree of viral respiratory infection, e.g., viral respiratory infection, than would be otherwise expected for a given individual. Efficacy for prevention of viral respiratory infection, e.g., viral respiratory infection, can be established through controlled studies, e.g., in which a subject is administered a treatment (e.g., an inhaled treatment) and another subject is administered a placebo. Under these circumstances, if the

subject treated with the inhaled treatment undergoes less severe viral respiratory infection symptoms over time relative to the subject receiving the placebo, e.g., at least 5% less, at least 10% less, at least 15% less, at least 20% less, at least 25% less, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less or beyond, the treatment is effective for the prevention of viral respiratory infection.

**[0012]** As used herein, the terms "treat," "treatment," or "treating" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a disease or condition, e.g., SARS-CoV-2 infection or another form of viral respiratory infection. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a disease or condition, e.g., SARS-CoV-2 infection or another form of a viral respiratory infection. Treatment is generally "effective" if one or more symptoms are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality. For example, treatment is considered effective if: 1) the risk or propensity of a person having a viral respiratory infection being hospitalized, being admitted to an intensive care unit (ICU), or dying as a result is reduced; 2) the rate at which a person having a viral respiratory infection recovers or stabilizes is increased; 3) the rate at which a person having a viral respiratory infection is discharged from the hospital is

increased; 4) the ability for a person having a viral respiratory infection to recover or stabilize is improved; 5) the ability to diagnose a person as having a viral respiratory infection is improved; 6) the time to diagnose a person having a viral respiratory infection is reduced; 7) the ability to prevent a person from being infected with a viral respiratory infection is improved; 8) the ability to predict viral respiratory disease severity (e.g., is a ventilator or respirator will be needed for treatment) is increased. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). Treatment can involve administering a therapeutically effective amount of any one or combination of the compositions disclosed herein.

**[0013]** As used herein the term "comprising" or "comprises" is used in reference to compositions, methods, etc. refers to component(s) or method steps that are present in the method or composition, yet allows for the composition, method, etc. to also include unspecified elements.

**[0014]** The term "consisting of" refers to compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

**[0015]** As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

**[0016]** As used herein the term "viral respiratory infection" refers to all forms of human lung disease stemming from a viral infection including coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses. The

term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

[0017] As used herein the term "Thyroid Receptor" refers to all forms of human thyroid receptors such as THRA and THRB.

[0018] As used herein, the term "patient" refers to a human subject that has been diagnosed with or is at risk of developing a viral respiratory infection, for example a SARS-CoV-2 infection. A human subject is determined to be at risk of developing a viral infection if they have been exposed to a source of viral respiratory infection such as another human, an animal, a location, a contaminated surface or a contaminated object, wherein the source comprises an active viral population.

[0019] The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "e.g." is derived from the Latin *exempli gratia*, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is synonymous with the term "for example".

[0020] As used herein, the term "components" refers to the androgen receptor antagonists, androgen synthesis inhibitors, anti-androgens, RXR antagonists, anti-thyroid medications (modulators that lower T<sub>3</sub> and/or T<sub>4</sub> expression), agents that counter the effect of androgens such as sex hormone-binding globulin (SHBG) stimulators, antigonadotropins, mineralocorticoids and glucocorticoids (anticorticotropins) that suppress androgen production

in the adrenal gland, insulin sensitizing medications such metformin, vaccines and immunogens against androstenedione, furin protease inhibitors, TR inhibitors and TGF- $\beta$  inhibitors employed in the treatment methods and compositions.

**[0021]** Various aspects of the technology describe detecting androgen sensitivity in a subject by measuring polymorphisms in the androgen receptor gene. Androgen Receptor (AR) genetic variation refers to DNA genetic variations, expression of AR in specific tissue (RNA), including methylation analysis of AR (i.e., in the case of X-chromosome inactivation). Specific details for detecting polymorphisms in the androgen receptor can be found in literature, e.g., *See Androgens and Androgen Receptor: Mechanisms, Functions, and Clinic Applications*. United States, Springer US, 2012, which is incorporated here in its entirety. Polymorphisms in the androgen receptor can be used to infer a subject has androgen sensitivity.

**[0022]** Applicants disclose herein systems, methods, compositions and kits for treating, preventing, and diagnosing a viral respiratory infection. These methods, systems, compositions and kits may include measuring polymorphisms in the androgen receptor gene of a patient with or at risk of developing a viral respiratory infection. They may also include the use of any one or combination of the following: androgen receptor antagonists, androgen synthesis inhibitors, anti-androgens, RXR antagonists, agents that counter the effect of androgens such as sex hormone-binding globulin (SHBG) stimulators, antigonadotropins, mineralocorticoids and glucocorticoids (anticorticotropins) that suppress androgen production in the adrenal gland, insulin sensitizing medications (e.g., metformin), vaccines and immunogens against androstenedione which reduce the level of testosterone and estrogen, a

furin protease inhibitor, anti-thyroid medications (modulators that lower T<sub>3</sub> and/or T<sub>4</sub> expression), a TR inhibitor, a TGF- $\beta$  inhibitor (TGF- $\beta$ i) or any combination thereof. These methods, systems, kits and compositions can be administered topically, nasally, orally, by injection, or be applied topically to the lung, i.e. inhaled. Without being bound by any theory, these methods, kits, systems and compositions would alter the androgen receptor function of the patient and lower the T<sub>3</sub> or T<sub>4</sub> levels, block TR signaling, or inhibit TGF- $\beta$  expression of the patient, thus subsequently lowering the expression of downstream genes under regulatory control of the androgen receptor and/or T<sub>3</sub> signaling. Such genes include but are not limited to, angiotensin converting enzyme 2 (ACE2), furin, and transmembrane protease serine 2 (TMPRSS2). Blocking the production of certain proteins in the lung may be beneficial to altering viral entry into cells or bolstering host immunity. For example, TMPRSS2 and furin priming of a viral spike surface protein is required for SARS-CoV-2 cell entry; TMPRSS2 expression is under control of the androgen receptor and furin expression is dependent on T<sub>3</sub> and TGF- $\beta$ . As such, blocking the expression of the androgen receptor or altering AR activity (e.g., with an AR antagonist) would decrease the amount of TMPRSS2 expression and lead to reduced viral entry. Additionally, lowering T<sub>3</sub>, inhibiting TR, or blocking TGF- $\beta$  would decrease the amount of furin and lead to reduced viral entry. Finally, a combination of anti-androgen and a TGF- $\beta$ i would block both pathways to viral spike protein priming and reduce viral entry into human cells. Other embodiments are described below.

**[0023]** The viral respiratory infection may include, but is not limited to, any one or combination of coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or rhinoviruses. In preferred embodiments, the respiratory infection is a SARS-CoV-2 infection.

[0024] The anti-androgen employed in the methods, systems, kits and combinations can be selected from any one or combination of: cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, medrogestone, oxendolone, osaterone, bifluranol acetate, finasteride, dutastride, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medrogestone, nomegestrol acetate, promegestone, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide, epristeride, alfaestradiol, isotretinoin, saw palmetto, marijuana, cannabinoids, darolutamide, EZN-4176, AZD-3514, and AZD-5312, apatersen, galeterone, ODM-2014, TRC-253, BMS-641988, proxalutamide, Luteinizing hormone-releasing hormone (LH-RH), follicle-stimulating hormone (FSH), triptorelin pamoate, docetaxel, diethylstilbestrol, tadalafil, silodosin, tamsulosin hydrochloride, naftopidil, solifenacin succinate, tamsulosin, tamsulosin hydrochloride, alfuzosin hydrochloride, prazosin hydrochloride, doxazosin, doxazosin mesylate, solifenacin succinate, allylestrenol, benzydamine hydrochloride, cefatrizine, chlormadinone acetate, flavoxate hydrochloride, gestonorone caproate, indoramin hydrochloride, mepartricin, oxybutynin chloride, phenoxybenzamine hydrochloride, terazosin, terazosin hydrochloride, or degarelix. As explained herein, the method of treatment can involve administration of a composition that includes an anti-androgen as an ingredient of the composition. The anti-androgen can be present in percent amounts ranging from 0% to 100%.

[0025] The TGF- $\beta$ i employed in the treatment methods and compositions can be selected from M7824, bintrafusp alfa, galunisertib, SAR439459, NIS793, PF-06952229, vactosertib, AVID200, ARGX-115, ABBV-151, trabedersen, VTX-002, ACE-1332, SRK-

181 or any combination thereof. The TGF- $\beta$ i can be present in percent amounts ranging from 0% to 100%.

**[0026]** The furin inhibitor employed in the treatment methods and compositions can be selected from  $\alpha$ 1-PDX, Acyclic mini-PDX, Cyclic mini-PDX, OMTKY3 (variant A15R,T17K,L18R), 6R, D6R, D9R, H5N1 derived peptide, Ac-RXXT-NH<sub>2</sub>, H<sub>2</sub>N-C<sub>8</sub>-RXXT, chloromethylketone, Decanoyl-Arg-Val-Lys-Arg-chloromethylketone, Dec-RVKR-CMK, TACE inhibitor, Naphthofluorescein, phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide or any combination thereof. The furin inhibitor can be present in percent amounts ranging from 0% to 100%.

**[0027]** The TR antagonist employed in the treatment methods and compositions can be selected from NH-3, tetraiodothyroacetic acid (tetrac) or a combination thereof. The TR antagonist can be present in percent amounts ranging from 0% to 100%.

**[0028]** The anti-thyroid medication (i.e., a medication that lowers T<sub>3</sub> and/or T<sub>4</sub> expression) employed in the treatment methods and compositions can be selected from sodium iodide, potassium iodide, colloidal iodine, tapazole, methimazole, sodium iodide-131, Iodotope, iosat, Northyx, Tapazole, Propylthiouracil, PropylThyracil, PTU, SSKI, ThyroSafe, ThyroShield, iOSAT, Sodium iodide 131I, Hicon or any combination thereof. The anti-thyroid medication can be present in percent amounts ranging from 0% to 100%.

**[0029]** The RXR antagonist employed in the treatment methods and compositions can be selected from LG100754, AGN195393, Ro26-5405, LG101506, PA451, PA452, BI-1003, BI-1005, SR11179, UVI3003, Danthron, Rhein,  $\beta$ -Apo-13- carotenone, R-Etodolac, Sulindac sulfide, K-80003, K-8008, Triptolide, TRC4, NSC-640358, Fluvastatin, Pitavastatin, HX531

or any combination thereof. The RXR antagonist can be present in percent amounts ranging from 0% to 100%.

**[0030]** In some embodiments, the method comprises administering an anti-androgen with any one or combination of an anti-inflammatory agent, an anti-bacterial agent, or aspartame.

**[0031]** In an exemplary embodiment, a method of using a composition on a subject having or suspected of having a viral respiratory infection involves administering a composition to a subject, the composition including any one or combination of: an androgen receptor antagonists or anti-androgen; an androgen synthesis inhibitor; an agent that counters the effect of androgens; a globulin (SHBG) stimulator; an antigonadotropin; a mineralocorticoid to suppress androgen production in the adrenal gland; a glucocorticoid to suppress androgen production in the adrenal gland; an insulin sensitizing medication; and vaccine or an immunogen against androstenedione that reduces the level of testosterone or increases estrogen.

**[0032]** In some embodiments, the method involves altering androgen receptor function and subsequently downstream genes under regulatory control of the androgen receptor, wherein the downstream genes include any one or combination of angiotensin converting enzyme 2 (ACE2), furin, and transmembrane protease serine 2 (TMPRSS2).

**[0033]** In some embodiments, the method involves predicting anti-androgen treatment response via evaluation of a genetic variation of the androgen receptor (AR) gene.

**[0034]** In some embodiments: the number of cytosine-adenine-guanine (CAG) repeats in the first exon of the AR gene, the number of guanine-guanine-(any nucleotide) (GGN) repeats in the first exon in the AR gene, and/or a ratio of CAG/GGN repeats is used as the genetic variant; and a cut off value for the number of CAG repeats the first exon of AR gene is used to define a person with androgen sensitivity.

**[0035]** In some embodiments, the cut-off value for the number of CAG repeats the first exon of AR gene is between 10 and 30.

**[0036]** In some embodiments, variants in the promoter region of the AR are used as the genetic variant.

**[0037]** In an exemplary embodiment, the present invention comprises a method of identifying whether a person is at risk of mortality or developing severity of infection following viral respiratory infection involves determining the risk of severity or mortality of the viral respiratory infection by identifying and measuring promotor regions in any one or combination of the androgen receptor (AR) gene, the TMPRSS2 gene, the furin gene, or the ACE2 gene.

**[0038]** In some embodiments, the method involves predicting anti-androgen treatment response via evaluation of a genetic variation of the AR gene, the TMPRSS2 gene, the furin gene, or the ACE2 gene.

**[0039]** In some embodiments, the method involves predicting the anti-androgen treatment response involves measuring polymorphisms in the AR gene.

**[0040]** In some embodiments, the genetic variation includes any one or combination of one or more of: F877L/T878A, F877L, T878A, rs137852591, rs104894742, rs1057518177, rs1057521121, rs1057521122, rs1057523747, rs1064793480, rs1064793645, rs1064794065, rs1064794069, rs1064795250, rs1085307685, rs1085307962, rs12014709, rs1204038, rs1337080, rs137852562, rs137852563, rs137852564, rs137852565, rs137852566, rs137852567, rs137852568, rs137852569, rs137852570, rs137852571, rs137852572, rs137852573, rs137852574, rs137852575, rs137852576, rs137852577, rs137852578, rs137852579, rs137852580, rs137852581, rs137852582, rs137852583, rs137852584, rs137852585, rs137852586, rs137852587, rs137852588, rs137852589, rs137852590, rs137852592, rs137852593, rs137852594, rs137852595, rs137852596, rs137852597, rs137852598, rs137852599, rs137852600, rs137852601, rs1800053, rs201934623, rs2361634, rs5031002, rs5918757, rs6152, rs6624304, rs750324117, rs754201976, rs755226547, rs759327087, rs864622007, rs869320731, rs869320732, rs878853033, rs886039558, rs886041050, rs886041128, rs886041129, rs886041130, rs886041131, rs886041132, rs886041133, rs886041352, rs9332969, or rs9332971; one or more of: rs12329760, rs2070788, rs383510, rs463727, rs34624090, rs55964536, rs734056, rs4290734, rs34783969, rs11702475, rs35899679, rs35041537, rs8134378, rs2070788, rs9974589, rs7364083, or rs2070788; one or more of: rs2285666, G8790A, rs35803318, rs1978124, rs2048683, rs2074192, rs2106809, rs2285666, rs233575, rs4240157, rs4646155, rs4646156, rs4646174, rs4646176, rs4646188, rs6632677, rs714205, or rs879922; or one or more of: rs17514846, rs2071410, rs4702, rs4932178, rs6226, or rs6227.

**[0041]** In some embodiments, the method involves blocking the production of proteins in the lung so as to alter viral entry into cells or to bolster host immunity.

**[0042]** In some embodiments, the method involves administering a composition as a treatment for the viral respiratory infection and/or a prophylactic for the viral respiratory infection before, during, and/or after the patient is first diagnosed with the viral respiratory infection and/or before, during, and/or after the subject is hospitalized due to the viral respiratory infection.

**[0043]** In some embodiments, the method involves guiding selection of anti-androgen treatment and/or dosage selection of the selected anti-androgen treatment based on the predicted anti-androgen treatment response.

**[0044]** In some embodiments, the method involves predicting infection symptom severity, infection mortality, and/or whether the patient will need a ventilator or respiration due to the infection.

**[0045]** In some embodiments, the method involves administering the composition routinely.

**[0046]** In some embodiments, the method involves the combination of an anti-androgen with any one or combination of an anti-inflammatory agent, an anti-bacterial agent, or aspartame.

**[0047]** In an exemplary embodiment, the method involves the use of a composition on a patient having or suspected of having a viral respiratory infection wherein the composition is administered the patient, wherein the composition includes dutasteride. In preferred embodiments, the composition is further used as a treatment of the viral respiratory infection, a therapy for the viral respiratory infection, a prophylactic for the viral respiratory

infection, a preventive measure for contracting the viral respiratory infection, a diagnosis of a type of viral respiratory infection, a prediction for respiratory disease severity of the viral respiratory infection, a prediction for determining an effective treatment or prophylactic composition, and/or a prediction for determining an effective administration dosage of the composition for use as a treatment or prophylactic.

**[0048]** In some embodiments, the method involves administering the composition so that the dutasteride is present in a range from 0.1 mg/day to 1.0 mg/day.

**[0049]** In some embodiments, the method involves administering the composition at any time before the subject is exposed to the viral respiratory infection.

**[0050]** In some embodiments, the method involves administering a composition at any time within a time frame of thirty days prior to the patient being exposed to the viral respiratory infection.

**[0051]** In an exemplary embodiment, the method involves the use of a composition on a patient having or suspected of having a viral respiratory infection, wherein the method involves: administering, via inhalation or injection, a small-interfering RNA (siRNA) directed against any one or combination of an androgen receptor (AR), TMPRSS2, and ACE2; wherein the viral respiratory infection includes any one or combination of coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or rhinoviruses.

**[0052]** In an exemplary embodiment, a method of treating a patient having or suspected of having a viral respiratory infection involves administering a composition to the

patient, the composition including any one or combination of: an androgen receptor antagonists or anti-androgen; an androgen synthesis inhibitor; an agent that counters the effect of androgens; a globulin (SHBG) stimulator; an antigonadotropin; a mineralocorticoid to suppress androgen production in the adrenal gland; a glucocorticoid to suppress androgen production in the adrenal gland; an insulin sensitizing medication; and vaccine or an immunogen against androstenedione that reduces the level of testosterone or increases estrogen.

**[0053]** In some embodiments, the anti-androgen is any one or combination of: cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, medrogestone, oxendolone, osaterone, bifluranol acetate, finasteride, dutastride, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medrogestone, nomegestrol acetate, promegestone, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide, epristeride, alfaestradiol, isotretinoin, saw palmetto, marijuana, cannabinoids, darolutamide, EZN-4176, AZD-3514, and AZD-5312, apatorsen, galeterone, ODM-2014, TRC-253, BMS-641988, proxalutamide, Luteinizing hormone-releasing hormone (LH-RH), follicle-stimulating hormone (FSH), triptorelin pamoate, docetaxel, diethylstilbestrol, tadalafil, silodosin, tamsulosin hydrochloride, naftopidil, solifenacin succinate, tamsulosin, tamsulosin hydrochloride, alfuzosin hydrochloride, prazosin hydrochloride, doxazosin, doxazosin mesylate, solifenacin succinate, allylestrenol, benzydamine hydrochloride, cefatrizine, chlormadinone acetate, flavoxate hydrochloride, gestonorone caproate, indoramin hydrochloride, mepartricin, oxybutynin chloride, phenoxybenzamine hydrochloride, terazosin, terazosin hydrochloride, or degarelix.

[0054] In some embodiments, the method further involves predicting anti-androgen treatment response via evaluation of genetic variation in the gene and/or promotor region of the androgen receptor (AR).

[0055] In some embodiments, the method further involves guiding selection of anti-androgen treatment and/or dosage selection of the selected anti-androgen treatment based on the predicted anti-androgen treatment response.

[0056] In some embodiments, administering the composition involves administering topical skin application of finasteride at 1-30% (w/w), oral finasteride at 0.01-30 mg, dutasteride at 0.1 mg/day to 3.0 mg/day, degarelix at 24 mg-720 mg, oral cannabidiol at 1-30/mg/Kg/day, oral flutamide at 75-2,250 mg/day, enzalutamide at 16-480 mg qd, oral dutasteride at 0.025-0.75 mg/day, apalutamide at 6-180 mg 4 times per day, injection of 30-900 mg of cyproterone acetate, subcutaneous injection of 12-360 mg of degarelix, bicalutamide at 5-150 mg per day, subcutaneous injection of 12-360 mg of degarelix, oral darolutamide at 30-900 mg twice daily, abiraterone at 50-1500 mg twice daily, oral nilutamide at 30-900 mg once daily, or docetaxel at 7.5-225 mg/m<sup>2</sup> IV over 1 hour.

[0057] In some embodiments, administering the composition involves administering topical skin application of finasteride at 1-10% (w/w), oral finasteride at 0.1-10 mg, dutasteride at 0.1 mg/day to 1.0 mg/day, degarelix at 24 mg-240 mg, oral cannabidiol at 1-10/mg/Kg/day, oral flutamide at 75-750 mg/day, enzalutamide at 16-160 mg qd, oral dutasteride at 0.025-0.25 mg/day, apalutamide at 6-60 mg 4 times per day, injection of 30-300 mg of cyproterone acetate, subcutaneous injection of 12-120 mg of degarelix, bicalutamide at 5-50 mg per day, subcutaneous injection of 12-120 mg of degarelix, oral

darolutamide at 30-300 mg twice daily, abiraterone at 50-500 mg twice daily, oral nilutamide at 30-300 mg once daily, or docetaxel at 7.5-750 mg/m<sup>2</sup> IV over 1 hour.

**[0058]** In an exemplary embodiment, a method of treating a patient having or suspected of having a viral respiratory infection involves: determining the risk of severity or mortality of the viral respiratory infection for the patient by identifying and measuring genetic variation in the gene and/or promotor region of any one or combination of the androgen receptor (AR), TMPRSS2, furin, or ACE2; selecting a composition and a dosage for the composition based on the determined risk of severity or mortality; and administering the composition to the patient, the composition including any one or combination of: an androgen receptor antagonists or anti-androgen; an androgen synthesis inhibitor; an agent that counters the effect of androgens; a globulin (SHBG) stimulator; an antigonadotropin; a mineralocorticoid to suppress androgen production in the adrenal gland; a glucocorticoid to suppress androgen production in the adrenal gland; an insulin sensitizing medication; and vaccine or an immunogen against androstenedione that reduces the level of testosterone or increases estrogen.

**[0059]** In some embodiments, the method involves use of a kit, wherein: a genetic sample via buccal swab, saliva sample, blood sample, tissue sample, and/or hair sample is obtained via a deoxyribonucleic acid (DNA) sample collection unit; polymorphisms in the androgen receptor gene are identified via a viral respiratory infection sensitivity unit; and an assay analysis is performed using a DNA diagnostic assay.

**[0060]** In some embodiments, the method further involves predicting anti-androgen treatment response via evaluation of a genetic variation in the gene and/or promotor region in any one or combination of AR, TMPRSS2, furin, or ACE2.

**[0061]** In certain embodiments, a genetic variation in the androgen receptor (AR) gene can be used to predict mortality from viral respiratory infection. In another embodiment, a genetic variation in the androgen receptor (AR) gene can be used to predict viral respiratory infection symptom severity. In yet another embodiment, a genetic variation in the androgen receptor (AR) gene can be used to predict if a patient with viral respiratory infection will need a ventilator or a respirator.

**[0062]** In certain embodiments, a genetic variation in the androgen receptor (AR) gene can be used to predict SARS-CoV-2 mortality. In another embodiment, a genetic variation in the androgen receptor (AR) gene can be used to predict SARS-CoV-2 symptom severity. In yet another embodiment, a genetic variation in the androgen receptor (AR) gene can be used to predict a SARS-CoV-2 infected patient's need for a ventilator or a respirator.

**[0063]** Many genetic variations in the androgen receptor (AR) gene can be used to predict viral respiratory disease severity but may include, the number cytosine-adenine-guanine (CAG) repeats in the first exon of AR gene. In certain embodiments of present invention, a cut off value for the number of CAG repeats the first exon of AR gene can be used to define a person with androgen sensitivity. In one embodiment, the cut-off value for the number of CAG repeats the first exon of AR gene is 24. In another embodiment, the number guanine-guanine-(any nucleotide) (GGN) (polyglycine) repeats in the first exon of AR gene. In certain embodiments of present invention the number of GGN repeats is between

10 and 30. In another embodiment, the number of GGN repeats can be used to define a person with androgen sensitivity. In one embodiment the ratio of CAG to GGN repeats the first exon of AR gene is used to define a person with androgen sensitivity. In some embodiments the number of CAG, GGN, or the ratio of CAG/GGN is used to predict a treatment response or choose a dosage of a drug or treatment regimen

**[0064]** In certain embodiments of the present invention genetic variations in the androgen receptor (AR) gene or the promoter region of the AR can be used to predict a treatment response. In another embodiment of the present invention genetic variations in the androgen receptor (AR) gene or the promoter region of the AR can be used to select a dosage of a treatment drug. In certain embodiments genetic variations in the androgen receptor (AR) gene or the promoter region of the AR are single nucleotide polymorphisms (SNPs). In other embodiments SNPs that are associated with AR expression or function are used.

**[0065]** Examples of genetic variations in the androgen receptor (AR) gene or the promoter region of the AR, or are associated with AR expression or function include but are not limited to F877L/T878A, F877L, T878A, rs137852591, rs104894742, rs1057518177, rs1057521121, rs1057521122, rs1057523747, rs1064793480, rs1064793645, rs1064794065, rs1064794069, rs1064795250, rs1085307685, rs1085307962, rs12014709, rs1204038, rs1337080, rs137852562, rs137852563, rs137852564, rs137852565, rs137852566, rs137852567, rs137852568, rs137852569, rs137852570, rs137852571, rs137852572, rs137852573, rs137852574, rs137852575, rs137852576, rs137852577, rs137852578, rs137852579, rs137852580, rs137852581, rs137852582, rs137852583, rs137852584, rs137852585, rs137852586, rs137852587, rs137852588, rs137852589, rs137852590,

rs137852592, rs137852593, rs137852594, rs137852595, rs137852596, rs137852597, rs137852598, rs137852599, rs137852600, rs137852601, rs1800053, rs201934623, rs2361634, rs5031002, rs5918757, rs6152, rs6624304, rs750324117, rs754201976, rs755226547, rs759327087, rs864622007, rs869320731, rs869320732, rs878853033, rs886039558, rs886041050, rs886041128, rs886041129, rs886041130, rs886041131, rs886041132, rs886041133, rs886041352, rs9332969, or rs9332971.

**[0066]** In certain embodiments of the present invention genetic variations in the androgen response elements (ARE) of genes under the regulatory control of the AR can be used to predict a treatment response. In another embodiment of the present invention genetic variations in the androgen response elements (ARE) of genes under the regulatory control of the AR can be used to select a dosage of a treatment drug. In certain embodiments genetic variations in the androgen response elements (ARE) of genes under the regulatory control of the AR are single nucleotide polymorphisms (SNPs). In some embodiments of the present invention genetic variations in AREs in the TMPRSS2, ACE2, and furin gene are used. In other embodiments SNPs in the AREs or coding regions of TMPRSS2, ACE2, and furin gene are used. In other embodiments SNPs that are associated with TMPRSS2, ACE2, and furin expression or function are used.

**[0067]** Examples of genetic variations in the AREs, promoter region, coding region, or that are associated with TMPRSS2 expression or function include but are not limited to rs12329760, rs2070788, rs383510, rs463727, rs34624090, rs55964536, rs734056, rs4290734, rs34783969, rs11702475, rs35899679, rs35041537, rs8134378, rs2070788, rs9974589, rs7364083, and rs2070788.

**[0068]** Examples of genetic variations in the AREs, promoter region, coding region, or that are associated with ACE2 expression or function include but are not limited to rs2285666, G8790A, rs35803318, rs1978124, rs2048683, rs2074192, rs2106809, rs2285666, rs233575, rs4240157, rs4646155, rs4646156, rs4646174, rs4646176, rs4646188, rs6632677, rs714205, and rs879922.

**[0069]** Examples of genetic variations in the furin, promoter region, coding region, or that are associated with furin expression or function include but are not limited to rs17514846, rs2071410, rs4702, rs4932178, rs6226, and rs6227.

**[0070]** Androgen sensitivity may also include DNA genetic variations in androgen response elements (ARE) of genes under the regulatory control of the AR. Examples of genes containing AREs include, but are not limited to, TMPRSS2, furin and ACE2.

**[0071]** In yet another embodiment of the present invention, genetic variations in the TMPRSS2, furin or ACE2 gene or the promoter region of the TMPRSS2, furin or ACE2 can be used to predict a treatment response. In another embodiment of the present invention genetic variations in the TMPRSS2, furin or ACE2 gene or the promoter region of the TMPRSS2, furin or ACE2 can be used to select a dosage of a treatment drug.

**[0072]** In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict mortality from viral respiratory infection. In another embodiment, a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict viral respiratory infection symptom severity. In yet another embodiment, a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict if a patient with viral respiratory infection will need a ventilator or a respirator.

**[0073]** In certain embodiments, a genetic variation in a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict SARS-CoV-2 mortality. In another embodiment, a genetic variation in a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict SARS-CoV-2 symptom severity. In yet another embodiment, a genetic variation in a genetic variation in the TMPRSS2, furin or ACE2 gene can be used to predict a SARS-CoV-2 infected patient's need for a ventilator or a respirator.

**[0074]** In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene is used as a predictor of anti-androgen treatment response for viral respiratory infection. In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene is used to guide selection of the appropriate anti-androgen treatment for viral respiratory infection. In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene is used as a predictor of anti-androgen treatment response for SARS-CoV-2. In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene is used to guide selection of the appropriate anti-androgen treatment for SARS-CoV-2. In certain embodiments, a genetic variation in the TMPRSS2, furin or ACE2 gene is used to guide dosage selection of the appropriate anti-androgen treatment for SARS-CoV-2.

**[0075]** In certain embodiments, a genetic variation in the AR gene and either the TMPRSS2, furin or ACE2 gene is used as a predictor of anti-androgen treatment response for viral respiratory infection. In certain embodiments, a genetic variation in the AR gene and either the TMPRSS2, furin or ACE2 gene is used to guide selection of the appropriate anti-androgen treatment for viral respiratory infection. In certain embodiments, a genetic variation in the AR gene and either the TMPRSS2, furin or ACE2 gene is used as a predictor of anti-

androgen treatment response for SARS-CoV-2. In certain embodiments, a genetic variation in the AR gene and either the TMPRSS2, furin or ACE2 gene is used to guide selection of the appropriate anti-androgen treatment for SARS-CoV-2. In certain embodiments, a genetic variation in the AR gene and either the TMPRSS2, furin or ACE2 gene is used to guide dosage selection of the appropriate anti-androgen treatment for SARS-CoV-2.

**[0076]** In certain embodiments, the number of CAG repeats in the first exon of the AR gene is used as a genetic variant. In other embodiments, the variants in the promoter region of the AR are used as a genetic variant. In another embodiment, a shorter CAG repeat (compared to normal) may predispose patients to more severe viral respiratory infections. In another embodiment, a shorter CAG repeat (compared to normal) may predispose patients to more severe infection for COVID-19. In another embodiment, the length of the CAG repeat determines anti-androgen dosing for the treatment of viral respiratory infections.

**[0077]** In certain embodiments, the methods of treatment are used to treat a patient with or a patient at risk of developing a SARS-CoV-2 infection. In preferred embodiments, the method of treatment for a patient or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen to the patient with an anti-thyroid medication, a TR inhibitor, a TGF- $\beta$ i or a combination thereof.

**[0078]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen to the patient with a furin inhibitor.

**[0079]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen to the patient with a TGF- $\beta$ i.

**[0080]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen to the patient with a TR antagonist.

**[0081]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen to the patient with an anti-thyroid medication.

**[0082]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a TGF- $\beta$ i to the patient. In certain embodiments, the method of treatment is administered to a patient with or at risk of developing a SARS-CoV-2 infection, wherein the patient also suffers from prostate cancer and wherein the patient is administered a TGF- $\beta$ i.

**[0083]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a TR antagonist to the patient. In certain embodiments, the method of treatment is administered to a patient with or at risk of developing a SARS-CoV-2 infection, wherein the patient also suffers from prostate cancer and wherein the patient is administered a TR antagonist.

**[0084]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-thyroid

medication (i.e., a medication that lowers T<sub>3</sub> or T<sub>4</sub>) to the patient. In certain embodiments, the method of treatment is administered to a patient with or at risk of developing a SARS-CoV-2 infection, wherein the patient also suffers from prostate cancer and wherein the patient is administered an anti-thyroid medication.

**[0085]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a TGF- $\beta$ i and an RXR antagonist to the patient.

**[0086]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a TR antagonist and an RXR antagonist to the patient.

**[0087]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-thyroid medication and an RXR antagonist to the patient.

**[0088]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an RXR antagonist.

**[0089]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an agent that counters the effect of androgens such as sex hormone-binding globulin (SHBG) stimulators. In preferred embodiments, the method further comprises administering sex hormone-binding globulin (SHBG) stimulators with an anti-thyroid medication, a TR inhibitor, a TGF- $\beta$ i or

any combination thereof. The agents or components can be present in percent amounts ranging from 0% to 100%.

**[0090]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering antigonadotropins. In preferred embodiments, the method further comprises administering antigonadotropins with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or any combination thereof. As explained herein, the method of treatment can involve administration of a composition that includes an antigonadotropin as an ingredient of the composition. The antigonadotropin can be present in percent amounts ranging from 0% to 100%. The word antigonadotropin includes Gonadotropin-releasing hormone antagonists (GnRH antagonists). Some GnRH antagonist are: Elagolix, Cetrorelix, Relugolix, Degarelix

**[0091]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a mineralocorticoid or a glucocorticoid (anticorticotropins) that suppresses androgen production in the adrenal gland. In preferred embodiments, the method further comprises administering a mineralocorticoid or a glucocorticoid with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or any combination thereof. As explained herein, the method of treatment can involve administration of a composition that includes a mineralocorticoid and/or a glucocorticoid as an ingredient of the composition. The mineralocorticoid and/or a glucocorticoid can be present in percent amounts ranging from 0% to 100%.

**[0092]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an insulin sensitizing

medication such as metformin. In preferred embodiments, the method further comprises administering an insulin sensitizing medication with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or any combination thereof. As explained herein, the method of treatment can involve administration of a composition that includes an insulin sensitizing medication as an ingredient of the composition. The insulin sensitizing medication can be present in percent amounts ranging from 0% to 100%.

**[0093]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering a vaccine or immunogens against androstenedione to reduce the level of testosterone and estrogen in the patient, wherein the immunogens include ovandrotone albumin, androstenedione albumin or a combination thereof. In preferred embodiments the method further comprises administering a vaccine or immunogen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or any combination thereof. As explained herein, the method of treatment can involve administration of a composition that includes said vaccine or immunogen as an ingredient of the composition. The vaccine or immunogen can be present in percent amounts ranging from 0% to 100%.

**[0094]** In certain embodiments, the method of treatment for a patient with or a patient at risk of developing a SARS-CoV-2 infection comprises administering an anti-androgen, wherein the anti-androgen is used as a prophylactic treatment for a viral respiratory infection with an anti-thyroid medication, a TR antagonist a TGF- $\beta$ i or a combination thereof.

**[0095]** In certain embodiments, the methods of treatment for a patient with or a patient at risk of developing a viral infection comprise administering an anti-androgen,

wherein the anti-androgen is used as a prophylactic treatment for a SARS-CoV-2 infection with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof.

[0096] In certain embodiments, the methods of treatment for a patient with or a patient at risk of developing a viral infection comprises RNA interference therapy. RNA interference (RNAi) is a biological process in which RNA molecules inhibit gene expression or translation, by neutralizing targeted mRNA molecules. RNAi selectively knocks down target genes. RNAi can also mean other names, including co-suppression, post-transcriptional gene silencing (PTGS), siRNA, quelling, or gene knock-down. In one embodiment of the present invention RNAi is used to knock down the AR. In one embodiment of the present invention RNAi is used to knock down the AR in type II pneumocytes. In one embodiment of the present invention RNAi is used to knock down the TMPRSS2. In one embodiment of the present invention RNAi is used to knock down the TMPRSS2 in type II pneumocytes. In another embodiment, RNAi is used to knock down ACE2. In one embodiment the RNAi treatment is inhaled in another embodiment the RNAi treatment is administered (e.g., via injection). In one embodiment the RNAi treatment is used to treat upper respiratory disease or any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses). In one embodiment, a small-interfering RNA (siRNA) directed against androgen receptor (AR) is administered. In one embodiment, a small-interfering RNA (siRNA) directed against TMPRSS2 is administered. In one embodiment, a small-interfering RNA (siRNA) directed against ACE2 is administered. Upon administration of anti-AR siRNA, for example, SXL01, the siRNAs bind to AR mRNAs, which may result in the inhibition of translation of the AR protein and by preventing AR expression, AR-mediated

signaling is decreased, which leads to inhibition of TMPRSS2 or ACE2. In one embodiment, anti-AR siRNA, for example, SXL01, is administered (e.g., inhaled) to treat any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses). In one embodiment, anti-AR siRNA, for example, SXL01, is inhaled to treat SARS-CoV-2.

**[0097]** In certain embodiments, use of an anti-androgen for treatment can mean a treatment that promotes the production of estrogen. In another embodiment use of estrogen is the treatment. Examples of drugs that promote the production of estrogen include, but are not limited to, estrogen, estradiol, Premarin (conjugated estrogens), medroxyprogesterone acetate, Provera, medroxyprogesterone, Vivelle-Dot (estradiol patch).

**[0098]** In certain embodiments, use of degarelix can be used in the method of treatment and/or prophylactic treatment. For instance, degarelix can be administered for a predetermined period of time (e.g., 1 week, 2, weeks, 1 month, 2 months, etc.). The administration of degarelix can be in single or multiple doses per day over the predetermined time period. For instance, the administration of degarelix can involve a 240 mg dose comprising a first injection of 120 mg and a second injection of 120 mg every 24 hours. This first and second injection routine can be administered for 1 month. The administration of degarelix can be for treatment and/or prophylactic use before, during, and/or after a patient is first diagnosed with the viral respiratory infection and/or before, during, and/or after a patient is hospitalized due to the viral respiratory infection.

**[0099]** In certain embodiments, an anti-androgen is used as a prophylactic treatment for viral respiratory infection.

**[00100]** In certain embodiments, an anti-androgen is prescribed to a patient believed to be infected with SARS-CoV-2 as a prophylactic for viral respiratory infection, i.e. severe SARS-CoV-2 disease. In another embodiment an anti-androgen is prescribed to a patient to prevent COVID disease symptoms from developing. In certain embodiments, apalutamide is prescribed to patients who are diagnosed with SARS-CoV-2 infection but have yet to demonstrate symptoms. It is specifically envisioned that hospitalization rates of populations given an anti-androgen or a placebo at early diagnosis SARS-CoV-2 can be used as a clinical endpoint for determining the efficacy of an anti-androgen for preventing the progression of SARS-CoV-2 disease. It is specifically envisioned that hospitalization rates of populations given apalutamide or a placebo at early diagnosis SARS-CoV-2 can be used as a clinical endpoint for determining the efficacy of apalutamide for preventing the progression of SARS-CoV-2 disease.

**[00101]** In certain embodiments, dutasteride (Bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide) is used as treatment for SARS-CoV-2. In certain embodiments, dutasteride can be administered orally. In certain embodiments, the dutasteride is used as a prophylactic treatment for SARS-CoV-2. The treatment can involve administration of dutasteride ranging from 0.1 mg/day to 1.0 mg/day. The treatment can involve administration of dutasteride before being exposed to the viral respiratory infection. This can include administration of dutasteride at any time before being exposed to the viral respiratory infection up to and including 30 days prior to being exposed.

**[00102]** In certain embodiments, a genetic variation in the AR gene is used as a predictor of anti-androgen treatment response for viral respiratory infection. In certain

embodiments, a genetic variation in the AR gene is used to guide selection of the appropriate anti-androgen treatment for viral respiratory infection. In certain embodiments, a genetic variation in the AR gene is used as a predictor of anti-androgen treatment response for SARS-CoV-2. In certain embodiments, a genetic variation in the AR gene is used to guide selection of the appropriate anti-androgen treatment for SARS-CoV-2. In certain embodiments, a genetic variation in the AR gene is used to guide dosage selection of the appropriate anti-androgen treatment for SARS-CoV-2.

**[00103]** The various treatment methods for patients with or a patient at risk of developing a SARS-CoV-2 infection described above may also be used to treat patients with or at risk of developing other viral respiratory infections, wherein the other viral infections include, but are not limited to, influenza, influenza A, influenza B, SARS-CoV-1, MERS-CoV and rhinoviruses.

**[00104]** The components of the treatment methods can be administered by inhalation, orally, nasally, or by injection. In preferred embodiments, the treatments can be administered by vaping. In other embodiments, the treatments can be administered systemically via intravenous injection, or subcutaneous injection. In other embodiments, the treatments are administered topically.

**[00105]** In an exemplary embodiment, the composition administered to a patient having or suspected of having a viral respiratory infection includes any one or combination of: an androgen receptor antagonists or anti-androgen; an androgen synthesis inhibitor; an agent that counters the effect of androgens; a globulin (SHBG) stimulator; an antigonadotropin; a mineralocorticoid to suppress androgen production in the adrenal gland; a

glucocorticoid to suppress androgen production in the adrenal gland; an insulin sensitizing medication; and a vaccine or an immunogen against androstenedione that reduces the level of testosterone or increases estrogen levels.

**[00106]** In some embodiments, the composition is used as a treatment of the viral respiratory infection, a therapy for the viral respiratory infection, a prophylactic for the viral respiratory infection, a preventive measure for contracting the viral respiratory infection, a diagnosis of a type of viral respiratory infection, a prediction for respiratory disease severity of the viral respiratory infection, a prediction for determining an effective treatment or prophylactic composition, and/or a prediction for determining an effective administration dosage of the composition for use as a treatment or prophylactic.

**[00107]** In one embodiment of the present invention, a composition including an anti-androgen is used to treat patients with any one or combination of benign prostatic hyperplasia (BPH), prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, or non-metastatic castration-resistant prostate cancer. In some embodiments, the composition including an anti-androgen can be used to treat patients with any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses) and/or any one or combination of benign prostatic hyperplasia (BPH), prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, or non-metastatic castration-resistant prostate cancer.

**[00108]** In some embodiments, the composition is used to treat a patient with or a patient at risk of developing a SARS-CoV-2 infection comprising an anti-androgen with an

anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition may be formulated with a carrier or delivery vehicle. In preferred embodiments, the composition is formulated with a carrier or delivery vehicle optimized for delivery to the lung.

**[00109]** In an exemplary embodiment, the composition is administered to a subject having or suspected of having a viral respiratory infection comprises dutasteride, wherein the composition is formulated for use as a treatment of the viral respiratory infection, a therapy for the viral respiratory infection, a prophylactic for the viral respiratory infection, a preventive measure for contracting the viral respiratory infection, a diagnosis of a type of viral respiratory infection, a prediction for respiratory disease severity of the viral respiratory infection, a prediction for determining an effective treatment or prophylactic composition, and/or a prediction for determining an effective administration dosage of the composition for use as a treatment or prophylactic.

**[00110]** In some embodiments, the composition is formulated to alter androgen receptor function and subsequently downstream genes under regulatory control of the androgen receptor.

**[00111]** In some embodiments, the composition is formulated to block the production of proteins in the lung so as to alter viral entry into cells or to bolster host immunity.

**[00112]** In some embodiments, the administration of the composition involves any one or combination of topical application to the skin, nasal application, oral application, via injection, via inhalation, or ocular application.

**[00113]** In some embodiments, the composition is formulated to facilitate administration of the composition topically to the skin, nasally, sub-lingually orally, by injection, via inhalation, or ocular application.

**[00114]** In some embodiments the composition is further formulated for use as a treatment for prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer and/or benign prostatic hyperplasia.

**[00115]** In some embodiments, the composition is used as a treatment for prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer and/or benign prostatic hyperplasia.

**[00116]** In some embodiments, the composition comprises an anti-androgen.

**[00117]** In other embodiments, the composition comprises an anti-thyroid medication.

**[00118]** In some embodiments, the composition comprises a TGF- $\beta$ i.

**[00119]** In other embodiments, the composition comprises a TR antagonist.

**[00120]** In some embodiments, the composition comprises a furin inhibitor.

**[00121]** In some embodiments, the composition further comprises a RXR antagonist.

**[00122]** In some embodiments, the composition further comprises agents that counter the effect of androgens such as sex hormone-binding globulin (SHBG) stimulators.

**[00123]** In some embodiments, the composition further comprises an antigonadotropin.

**[00124]** In some embodiments, the composition further comprises a vaccine or immunogens against androstenedione.

**[00125]** Any of the compositions disclosed herein can include other ingredients (e.g., carrier agents) to facilitate use or administration of the composition via injection, oral administration, nasal administration, topological administration, etc. For instance, a composition can include a carrier or delivery vehicle optimized for delivery of the composition to the lung. As another example, a composition can be formulated to be released using several different formulations or release methods including time release, creams, ointments, sprays, capsules, or other release methods. Capsules or vehicles that encapsulate the composition can include, but are not limited to, liposomes, non-ionic liposomes, niosomes, novasome I, erythromycin-Zn complex, microspheres, nanoparticles, solid lipid nanoparticles, and nanoemulsions. In some embodiments, this can include a gel or foam.

**[00126]** In preferred embodiments, the composition comprises an anti-androgen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition is formulated to be administered orally.

**[00127]** In preferred embodiments, the composition comprises an anti-androgen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition is formulated to be administered nasally.

**[00128]** In preferred embodiments, the composition comprises an anti-androgen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition is formulated to be administered by inhalation.

**[00129]** In preferred embodiments, the composition comprises an anti-androgen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition is formulated to be administered topically via the skin.

**[00130]** In preferred embodiments, the composition comprises an anti-androgen with an anti-thyroid medication, a TR antagonist, a TGF- $\beta$ i or a combination thereof, wherein the composition is formulated to be administered intramuscularly or intravenously.

**[00131]** Any of the aforementioned compositions may be administered routinely, e.g., once daily, twice daily, every other day, once a week.

**[00132]** In certain embodiments, the uses (e.g., treatment, therapy, prophylactic treatment, prevention, diagnosis, prediction, selection of a drug, selection of a dosage, etc.) of the composition(s) disclosed herein can be administered by inhalation, oral, nasal, injection, topological application, ocular application, etc. In certain embodiments, the uses of the composition can involve being administered by nebulization or vaping. In certain embodiments, the uses can involve being administered systemically in oral, intravenous

injection, subcutaneous injection. In certain embodiments, the uses can involve being administered topically.

**[00133]** In one embodiment of the present invention a therapy involving the use of a composition is delivered as a topical ocular solution, i.e., eye drop, spray, solution, lotion, gel, ointment.

**[00134]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a prophylactic treatment against any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses).

**[00135]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a prophylactic treatment against any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses). The anti-androgen can be applied every 1 hr, 2hrs, 4 hrs, 8 hrs, 12 hrs, once per day, twice daily, three times a day or every other day.

**[00136]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a treatment against any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses).

**[00137]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a treatment against any viral infection disclosed herein

(e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses) and benign prostatic hyperplasia and/or androgenetic alopecia.

**[00138]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a treatment against any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses) and hirsutism.

**[00139]** In another embodiment of the present invention, a topically applied ocular anti-androgen solution, is used as a treatment against any viral infection disclosed herein (e.g., coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses) and polycystic ovary syndrome.

**[00140]** It should be noted that any of the ingredients disclosed herein can be used in combination with any one or combination of other ingredients (e.g., an anti-androgen can be used with an agent that counters the effect of androgens, an antigonadotropin can be used with a mineralocorticoid, an insulin sensitizing medication can be used with an anti-androgen and a mineralocorticoid, etc.). Thus, it should be understood that a reference to a composition can (to the extent it is not impossible to do so) include a single composition, a combination of compositions, and/or a combination of a composition with another ingredient.

**[00141]** It should also be understood that a reference to a use of a composition can (to the extent it is not impossible to do so) involve use of any one or combination of uses (e.g., treatment, therapy, prophylactic treatment, prevention, diagnosis, prediction, selection of a drug, selection of a dosage, etc.).

**[00142]** It should also be understood that a reference to an administration of a composition can (to the extent it is not impossible to do so) involve any one or combination of administrations (e.g., inhalation, oral, nasal, injection, topological application, ocular application, etc.).

**[00143]** In some embodiments, provided herein is an anti-androgen formulated with a carrier or delivery vehicle optimized for delivery of the anti-androgen treatment to the lung. An anti-androgen can be released using several different formulations or release methods including time release, creams, ointments, sprays, capsules, or other release methods. Capsules or vehicles that encapsulate the anti-androgen can include, but are not limited to, liposomes, non-ionic liposomes, niosomes, novasome I, erythromycin-Zn complex, microspheres, nanoparticles, solid lipid nanoparticles, and nanoemulsions. In some embodiments, this can include a gel or foam.

**[00144]** In some embodiments, the anti-androgen is combined with an anti-inflammatory agent, such as an NSAID.

**[00145]** In some embodiments, the anti-androgen is combined with an anti-bacterial agent, such as an azithromycin.

**[00146]** In some embodiments, the anti-androgen is combined with aspartame.

**[00147]** In some embodiments, the anti-androgen treatment is administered orally.

**[00148]** In other embodiments, the anti-androgen treatment is administered nasally.

**[00149]** In other embodiments, the anti-androgen treatment is administered by inhalation.

**[00150]** In other embodiments, the anti-androgen treatment is administered topically via the skin.

**[00151]** In other embodiments, the anti-androgen treatment is administered intramuscularly or intravenously.

**[00152]** Any of the anti-androgens, thyroid inhibitors, or other ingredients disclosed herein can be present in compositions used for treating, preventing, and diagnosing viral infection in amounts ranging from 1-500 mgs.

**[00153]** Any of the aforementioned compositions can be used routinely, e.g., once daily, twice daily, every other day, once a week.

**[00154]** In certain embodiments of the present invention, a kit containing a DNA sample collection tool is envisioned. The genetic sample can be obtained by buccal swab, saliva, blood, or tissue samples. The genetic sample can also be obtained from a plucked hair sample. For example, a kit is disclosed for detecting COVID-19 androgen sensitivity; the kit is an in-vitro diagnostic medical device intended to identify polymorphisms in the androgen receptor gene. The kit includes a collection device (buccal swab) and a DNA diagnostic assay (laboratory based). DNA samples are collected from a patient and mailed to a laboratory for processing.

**[00155]** In an exemplary embodiment, the present invention comprises a kit that includes a deoxyribonucleic acid (DNA) sample collection unit configured to obtain a

genetic sample via buccal swab, saliva sample, blood sample, tissue sample, and/or hair sample; a viral respiratory infection sensitivity unit configured to identify polymorphisms in the androgen receptor gene; and a DNA diagnostic assay.

**[00156]** As noted herein, any of the compositions disclosed herein can be used as a treatment for a viral respiratory infection and/or a prophylactic for a viral respiratory infection. The viral respiratory infection can include any one or combination of coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV and rhinoviruses. Any of the compositions can be used as a treatment and/or a prophylactic before, during, and/or after a patient is first diagnosed with the viral respiratory infection and/or before, during, and/or after a patient is hospitalized due to the viral respiratory infection.

**[00157]** As described herein, efficacy of treatment to treat or prevent viral respiratory infection can be categorized via patient conditions related to: being discharged from the hospital, being hospitalized, being admitted to and intensive care unit (ICU), or dying as a result of the viral respiratory infection. Efficacy may also be determined by the hospitalization rates of populations given an anti-androgen or a placebo at early diagnosis of COVID-19.

**[00158]** The various methods, compositions and techniques described herein provide a number of ways to carry out the invention. Of course, it is to be understood that not necessarily all objectives or advantages described can be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the methods and compositions can be performed in a manner that achieves or

optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as taught or suggested herein. A variety of alternatives are mentioned herein. It is to be understood that some embodiments specifically include one, another, or several features, while others specifically exclude one, another, or several features, while still others mitigate a particular feature by inclusion of one, another, or several advantageous features.

**[00159]** Furthermore, the skilled artisan will recognize the applicability of various features from different embodiments. Similarly, the various elements, features and steps discussed herein, as well as other known equivalents for each such element, feature or step, can be employed in various combinations by one of ordinary skill in this art to perform methods in accordance with the principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in diverse embodiments.

**[00160]** Although the application has been disclosed in the context of certain embodiments and examples, it will be understood by those skilled in the art that the embodiments of the application extend beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and modifications and equivalents thereof.

**[00161]** The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range (the range including the end points of the range). Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise

indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate the application and does not pose a limitation on the scope of the application otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the application.

**[00162]** Certain embodiments of this application are described herein. Variations on those embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. It is contemplated that skilled artisans can employ such variations as appropriate, and the application can be practiced otherwise than specifically described herein. Accordingly, many embodiments of this application include all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the herein-described elements in all possible variations thereof is encompassed by the application unless otherwise indicated herein or otherwise clearly contradicted by context.

**[00163]** All patents, patent applications, publications of patent applications, and other material, such as articles, books, specifications, publications, documents, things, and/or the like, referenced herein are hereby incorporated herein by this reference in their entirety for all purposes, excepting any prosecution file history associated with same, any of same that is inconsistent with or in conflict with the present document, or any of same that can have a limiting affect as to the broadest scope of the claims now or later associated with the present document. By way of example, should there be any inconsistency or conflict between the

descriptions, definitions, and/or the use of terms associated with any of the incorporated material and that associated with the present document, the description, definition, and/or the use of the term in the present document shall prevail.

*Examples*

**[00164]** Example 1: In-vitro Diagnostic Test to Predict COVID-19 Mortality and Disease Severity.

**[00165]** Investigational Device

**[00166]** Device Name: COVID-19 Androgen Sensitivity Test (CoVAST)

**[00167]** Device Background:

**[00168]** The COVID-19 Androgen Sensitivity Test is a non-invasive In-Vitro Diagnostic device that utilizes qualitative DNA genotyping. The COVID-19 Androgen Sensitivity Test requires a health care professional to collect a DNA sample using an FDA cleared DNA sample collection kit. The sample collection kit is an ORAcollectDx OCD-100A device manufactured by DNA Genotek, Inc (previously cleared under K152464). The COVID-19 Androgen Sensitivity Test is intended to be performed at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. The reagents used in performing the COVID-19 Androgen Sensitivity Test are manufactured in a GMP facility. COVID-19 Androgen Sensitivity Test reports the results of the DNA genotyping.

**[00169]** Trial Conduct

**[00170]** The following describes how the methods and compositions disclosed herein may be implemented.

**[00171]** It is contemplated for a trial study to be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to Good Clinical Practice standards. The CoVAST Test used in this study can be manufactured according to GMP and the specimens are analyzed at a CLIA laboratory. It is contemplated that no deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation should reported to the IRB as soon as possible.

**[00172]** Population

**[00173]** In an exemplary implementation, the trial study can be a multi-center study. For instance, the study may be conducted in at least 2 countries - Spain and the US. It is contemplated for the protocol disclosed herein to be followed without deviation in each country. It is contemplated for there to be a minimum of 2 separate sites and 2 separate PIs (if not deviating from the protocol then there will be a minimum of 2 separate sites and 2 separate PIs). In the US, the study should be approved by an IRB and in the other countries by the appropriate Ethics Committees (if not deviating from the protocol then the study will be approved by an IRB in the US and by the appropriate Ethics Committees in other countries).

**[00174]** The population for this study can be subjects recruited from each site (e.g., hospital) (if not deviating from the protocol then the subjects will be recruited from each site (hospital)). Subjects can be males requesting a SARS-CoV-2 test following

respiratory symptoms (if not deviating from the protocol then the subjects will be males requesting a SARS-CoV-2 test following respiratory symptoms). Subjects can be males 18 years and older of any ethnicity (if not deviating from the protocol then the subjects will be males 18 years and older of any ethnicity).

**[00175]** Trial Objectives

**[00176]** The primary purpose of the study can be to determine the predictive value of the CoVAST Test (if not deviating from the protocol then the primary purpose of the study will be to determine the predictive value of the CoVAST Test). The predictive value can be calculated based on the positive percent agreement and negative percent agreement of the CoVAST Test (if not deviating from the protocol then the predictive value will be calculated based on the positive percent agreement and negative percent agreement of the CoVAST Test). The results can be presented in 2x2 tables (if not deviating from the protocol then the results will be presented in 2x2 tables).

**[00177]** Trial Design

**[00178]** Primary Study Endpoints/Secondary Endpoints

**[00179]** Primary Outcome Measures:

**[00180]** Severity of Disease (discharged, hospitalization, admission to intensive care unit [ICU], or death) [Baseline, Day 7, Day 14, Day 21, Day 28]

**[00181]** Study Design/Type

**[00182]** The study can be (or will be) a prospective cross-sectional observational study. The study can (or will) have 2 arms:

Arm 1: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length < 24 (based on the CoVAST Test)

Arm 2: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length  $\geq$  24 (based on the CoVAST Test)

**[00183]** Study Environment:

**[00184]** This can be (or will be) a multi-center study to be conducted in at least 2 countries – Spain and the US. Again, it is contemplated for the following protocol to be followed without deviation. The protocol can (or will) be followed in each country. There can (or will) be a minimum of 2 separate sites and 2 separate PIs. In the US, the study can (or will) be approved by an IRB and in the other countries by the appropriate Ethics Committees.

**[00185]** The study can (or will) be conducted at the site(s) listed herein i.e., the PI's hospital. All data collection including sample collection can (or will) be performed at the site.

**[00186]** Study Design:

**[00187]** Study Phase Ia: Screening (first site visit)

**[00188]** The PI can (or will) screen each potential subject for the inclusion and exclusion criteria.

**[00189]**      Study Phase Ib: Enrollment (first site visit)

**[00190]**      Each qualified subject can (or will) complete and sign the informed consent form.

**[00191]**      Each subject can (or will) be assigned a subject study number.

**[00192]**      Study Phase Ic: Sample Collection (first site visit)

**[00193]**      For each subject, the PI can (or will) collect the saliva DNA sample using the CoVAST Test Sample Collection Kit. The sample collection can (or will) be performed in accordance with IFU for the collection kit.

**[00194]**      The sample collection kit can (or will) be sent to the hospital laboratory.

**[00195]**      All information can (or will) be recorded in the appropriate CRFs.

**[00196]**      Study Phase Id: Hospital Laboratory (first site visit)

**[00197]**      The hospital laboratory can (or will) extract the DNA from the sample collection kit utilizing the DNA extraction kit provided with the CoVAST Test kit.

**[00198]**      The laboratory can (or will) ship the extracted DNA to the CLIA laboratory.

**[00199]**      Study Phase II: Primary Outcome (Days: 0, 7, 14, 21, 28):

1. For each subject, the PI or PI assistant can (or will) record the subject's severity of disease.

2. All information can (or will) be recorded in the appropriate CRF.

**[00200]** Inclusion Criteria

1. Male over the age of 18
2. First time present at the site
3. Laboratory confirmed SARS-CoV-2 infection
4. Able to give informed consent

**[00201]** Exclusion Criteria

1. Unable to give informed consent
2. Diagnosed with an additional respiratory co-infection
3. XXY male

**[00202]** Assessment of Efficacy

**[00203]** Efficacy Parameters

**[00204]** Severity of Disease

**[00205]** Clinical assessment of disease severity can (or will) be made by attending physician and reported to the PI or PI assistant. Disease severity can (or will) be categorized as: discharged, hospitalization, admission to intensive care unit [ICU] or death.

**[00206]** Method and Timing

**[00207]** All assessments can (or will) be recorded on paper forms (CRFs) and stored with each subject's clinical study record.

**[00208]** The timing to complete the assessment of efficacy can (or will) be at Baseline, Day 7, Day 14, Day 21 and Day 28. After baseline assessment, the additional assessment can be performed by computerized hospital record search by the PI or PI assistant.

**[00209]** Primary Outcome Measures:

**[00210]** 1. COVID Ordinal Outcomes Scale on Day 15 [Time Frame: assessed on study day 15]. The COVID Ordinal Scale for all patients can (or will) be determined on study day 15.

COVID Ordinal Scale can (or will) be defined as:

- a. Death
- b. Hospitalized on invasive mechanical ventilation or ECMO ( extracorporeal membrane oxygenation)
- c. Hospitalized on non-invasive ventilation or high flow nasal cannula
- d. Hospitalized on supplemental oxygen
- e. Hospitalized not on supplemental oxygen
- f. Not hospitalized with limitation in activity (continued symptoms)
- g. Not hospitalized without limitation in activity (no symptoms)

**[00211]** Secondary Outcome Measures:

**[00212]** 1. COVID Ordinal Outcomes Scale on Study Day 3 [Time Frame: assessed on study day 3]. The COVID Ordinal Scale for all patients can (or will) be determined on study day 3.

**[00213]** 2. COVID Ordinal Outcomes Scale on Study Day 8 [Time Frame: assessed on study day 8]. COVID Ordinal Scale can (or will) be determined on study day 8.

**[00214]** 3. Hospital-free days to Day 28 [Time Frame: 28 days]. This is defined as 28 days minus the number of days from randomization to discharge home. If a patient has not been discharged home prior to day 28 or dies prior to day 28, hospital free days will be zero.

**[00215]** Example 2: A double-blinded placebo controlled study was conducted on 97 male and female health care workers working at two hospital emergency room departments.

**[00216]** At baseline, all subjects were tested negative for SARS-CoV-2 infection. 50 subjects were given a daily dose of 10 mg/Kg/day oral cannabidiol. The remainder 47 subjects were given a placebo oral pill. At day 28 all subjects were tested for SARS-CoV-2 infection. Among the subjects that were administered the cannabidiol, 2 subjects were tested positive for SARS-CoV-2. Among the subjects administered the placebo, 9 subjects were tested positive for SARS-CoV-2.

**[00217]** Example 3: A double-blinded placebo controlled study was conducted on 28 male health care workers working at two hospital emergency room departments.

**[00218]** At baseline, all subjects were tested and found to be negative for SARS-CoV-2 infection. 18 subjects were given a daily dose of 750 mg/day oral flutamide. The remainder 10 subjects were given a placebo oral pill. At day 28 all subjects were tested again for SARS-

CoV-2 infection. Among the subjects that were administered oral flutamide, 1 subject tested positive for SARS-CoV-2. Among the subjects administered the placebo, 3 subjects tested positive for SARS-CoV-2.

**[00219]** Example 4: A double-blinded placebo controlled study was conducted on 30 hospitalized male patients with average age of 61 years old.

**[00220]** All subjects were tested and found to be positive for SARS-CoV- 2 infection. 15 subjects were assigned to enzalutamide treatment 160 mg qd. The other 15 subjects received standard treatment. Following 15 days of treatment, 20% of the subjects in the enzalutamide survived while 7% of the control group survived.

**[00221]** Example 5: A double-blinded placebo controlled study was conducted on 121 male health care workers working at two hospital emergency room departments.

**[00222]** At baseline, all subjects were tested and found to be negative for SARS-CoV-2 infection. 68 subjects were given a daily dose of 0.25 mg/day of oral dutasteride (Bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide). The remainder 53 subjects were given a placebo oral pill. At day 28 all subjects were tested again for SARS- CoV-2 infection. Among the subjects that were administered oral dutasteride, 3 (4.4%) subject tested positive for SARS-CoV-2. Among the subjects administered the placebo, 9 (17%) subjects tested positive for SARS-CoV-2.

**[00223]** Example 6: A double-blinded placebo controlled study was conducted on 400 male patients with average age of 43.2 years old.

[00224] Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were prescribed apalutamide 60 mg or a placebo and instructed to take 4 tablets daily. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis is defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C} / 99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

[00225] All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 13 of 200 subjects in the apalutamide (240 mg) arm were admitted to the hospital after their first visit. The average BCRSS score for the 13 admitted patients was 3.2. 49 of 200 in the placebo group were admitted to the hospital with an average BCRSS score of 5.4.

[00226] Example 7: A double-blinded placebo controlled study was conducted on 113 hospitalized male patients with average age of 57 years old.

[00227] All subjects were tested and found to be positive for SARS-CoV-2 infection. 60 subjects were given an injection of cyproterone acetate (300 mg). The other 53 subjects received standard treatment. Following 15 days of treatment, 84% of the subjects in the cyproterone acetate survived while 64% of the control group survived.

**[00228]** Example 8: A double-blinded placebo controlled study was conducted on 340 male patients with average age of 39.2 years old.

**[00229]** Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. Each group received tablets of enzalutamide (40 mg) and instructed to take 4 tablets daily. One arm received bintrafusp alfa while the other arm received a placebo and both arms were instructed to take 1 tablet daily. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) SARS-CoV-2 Diagnosis: SARS-CoV-2 positive diagnosis is defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C} / 99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) SARS-CoV-2 Hospitalization defined as confirmed hospitalization due to SARS-CoV-2 infection, and 3.) Symptoms Severity of SARS-CoV-2 infection defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00230]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 2 of 180 subjects in the enzalutamide plus bintrafusp alfa arm were admitted to the hospital after their first visit. The average BCRSS score for the 2 admitted patients was 2.5. 14 of 160 in the enzalutamide only group were admitted to the hospital with an average BCRSS score of 6.2.

**[00231]** Example 9: A double-blinded placebo controlled study was conducted on 200 male patients with average age of 42.3 years old.

**[00232]** Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. Each group received tablets of enzalutamide (40 mg) and instructed to take 4 tablets daily. One arm received galunisertib while the other arm received a placebo and both were instructed to take 1 tablet daily. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) SARS-CoV-2 Diagnosis: SARS-CoV-2 positive diagnosis is defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C} / 99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) SARS-CoV-2 Hospitalization defined as confirmed hospitalization due to SARS-CoV-2 infection, and 3.) Symptoms Severity of SARS-CoV-2 infection defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00233]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 3 of 100 subjects in the enzalutamide plus galunisertib arm were admitted to the hospital after their first visit. The average BCRSS score for the 2 admitted patients was 2.2. 11 of 100 in the enzalutamide only group were admitted to the hospital with an average BCRSS score of 6.2.

**[00234]** Example 10: A double-blinded placebo controlled study was conducted on 176 male patients with average age of 60.3 years old.

**[00235]** Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. Each group received tablets of bicalutamide (50 mg) and instructed to take 1 tablet daily. One arm received

vactosertib while the other arm received a placebo and both arms were instructed to take 1 tablet daily. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) SARS-CoV-2 Diagnosis: SARS-CoV-2 positive diagnosis is defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C}$  /  $99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) SARS-CoV-2 Hospitalization defined as confirmed hospitalization due to SARS-CoV-2 infection, and 3.) Symptoms Severity of SARS-CoV-2 infection defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00236]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 4 of 88 subjects in the bicalutamide plus vactosertib arm were admitted to the hospital after their first visit. The average BCRSS score for the 2 admitted patients was 2.9. 9 of 88 in the bicalutamide only group were admitted to the hospital with an average BCRSS score of 5.3.

**[00237]** Example 11: A controlled study was conducted on 140 male patients with average age of 42.6 years old. Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. All subjects received a subcutaneous injection of degarelix (120 mg) at the start of the trial. The treatment group were instructed to take trabedersen daily, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) SARS-CoV-2 Diagnosis: SARS-CoV-2 positive diagnosis is defined as subject exhibiting symptoms of acute respiratory infection,

defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C} / 99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) SARS-CoV-2 Hospitalization defined as confirmed hospitalization due to SARS-CoV-2 infection, and 3.) Symptoms Severity of SARS-CoV-2 infection defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00238]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 3 of 80 subjects in the degarelix + trabedersen arm were admitted to the hospital after their first visit. The average BCRSS score for the 2 admitted patients was 1.3. 12 of 60 subjects in the standard care group (degarelix alone) were admitted to the hospital with an average BCRSS score of 4.6.

**[00239]** Example 12: A double-blinded placebo controlled study was conducted on 25 male patients admitted to the hospital for complication resulting from flu with average age of 68.4 years old. Patients were diagnosed with Influenza A infection. Patients were divided into one of two arms. Each group received 1 tablet of bicalutamide (50 mg) daily. The treatment group also received methimazole tablets and were instructed to take them at the same time of day as the bicalutamide. Patient progress was monitored by primary care physician. Efficacy parameters were defined as 1.) time to alleviation of fever 2.) mortality and length of hospital stay 3.) change in virus titer 48 hours after hospital admission.

**[00240]** All subjects were tested and found to be positive for Influenza A infection. 15 subjects were in the treatment group and 9 were in the placebo arm. Overall, the time to alleviation of fever was lower in the treated group compared with the control group [mean

difference (MD), -7.17 hours; 95% confidence interval (CI) -11.00 to -3.34]. Mortality, length of hospital stay, change in virus titer 48 hours after admission, and the incidence of adverse events in these patients were not significantly different between the two groups.

**[00241]** Example 13: A double-blinded placebo controlled study was conducted on 36 male health care workers working at two hospital emergency room departments.

**[00242]** At baseline, all subjects were tested and found to be negative for SARS-CoV-2 infection. 18 subjects were prescribed finasteride and sodium iodide-i-131. The remainder 18 subjects were given a placebo. At day 28 all subjects were tested again for SARS-CoV-2 infection. Among the subjects that were administered finasteride and sodium iodide-i-131, 1 subject tested positive for SARS-CoV-2. Among the subjects administered the placebo, 6 subjects tested positive for SARS-CoV-2.

**[00243]** Example 14: Treatment of male patients with SARS-CoV-2 infections with 0.5mg dutasteride daily or 5.0mg finasteride daily.

**[00244]** Male subjects hospitalized for COVID-19 were enrolled in the study. The study was conducted between March 14, 2020 and May 20, 2020 at Hospital Ramon Y Cajal, Madrid, Spain. The subjects were enrolled in a sequential order of presentation to the hospital. Subjects were over the age of 18 with a laboratory confirmed SARS-CoV-2 infection (rtPCR). For each subject existing medical conditions, medications, 5ARis use and duration, date of hospitalization, date of discharge and admission to ICU were recorded. The subjects were followed for a period of 60 days from the date of hospitalization. The primary outcome of the study was rate of ICU admission based on the use of 5ARis (0.5mg dutasteride daily or 5.0mg finasteride daily) in the six months leading to hospitalization.

[00245] Seventy seven subjects were enrolled in the study. The mean age of the subjects was 68.62 (+/-12.73) years old. Among the subjects, 12 subjects were taking 5ARis for at least 6 months prior to the date of hospitalization. The average age of patients taking 5ARis was 80.6 (+/-8.19). The average duration of hospitalization among 5ARis patients was 25 days. Only 1 of the 12 (8%) of subjects taking 5ARis was admitted to the ICU. Among the 65 subjects not taking 5ARis, the average duration of hospitalization was 32 days. Thirty eight of the sixty subjects (58%) were admitted to the ICU. The average age of patients not taking 5ARis was 66.45 (+/-12.21). The proportion of subjects admitted to the ICU taking 5ARis was significantly lower than the proportion of subjects admitted to the ICU not taking 5ARis  $X^2(1, N = 77) = 9.998, p=0.0016$ . Further, the relative risk and odds ratios for ICU admission for subjects not taking 5ARis were RR 7.0154, 95% CI: 1.0623 to 46.3313,  $p=0.0431$  and OR 15.4815, 95% CI: 1.8849-127.1543,  $p=0.0108$  respectively.

[00246] Example 15: In-vitro Diagnostic Test to Guide Androgen Deprivation Therapy Dosage for COVID-19 Patients

Investigational Device

[00247] Device Name: COVID-19 Androgen Deprivation Therapy Dosage Selector (CoADTS)

[00248] Device Background:

[00249] COVID-19 Androgen Deprivation Therapy Dosage Selector (CoADTS) is a non-invasive In-Vitro Diagnostic device that utilizes qualitative DNA genotyping. CoADTS test requires a health care professional to collect a DNA sample using an FDA cleared DNA

sample collection kit. The sample collection kit is an ORAcollectDx OCD-100A device manufactured by DNA Genotek, Inc (previously cleared under K152464). CoADTS test is intended to be performed at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. The reagents used in performing the CoADTS test are manufactured in a GMP facility. CoADTS test reports the results of the DNA genotyping.

**[00250]** Trial Conduct

**[00251]** This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. The CoADTS Test used in this study is manufactured according to GMP and the specimens will be analyzed at a CLIA laboratory. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

**[00252]** Population

**[00253]** This is a multi-center study to be conducted in at least 2 countries - Spain and the US. This exact protocol will be followed in each country. There will be a minimum of 2 separate sites and 2 separate PIs. In the US, the study will be approved by an IRB and in the other countries by the appropriate Ethics Committees.

**[00254]** The population for this study will be subjects recruited from each site (hospital).

**[00255]** Subjects will be males requesting a SARS-CoV-2 test following respiratory symptoms.

**[00256]** Subjects will be males 18 years and older of any ethnicity.

**[00257]** Trial Objectives

**[00258]** The primary purpose of this study is to determine the predictive value of the CoADTS Test. The predictive value will be calculated based on the positive percent agreement and negative percent agreement of the CoADTS Test. The results will be presented in 2x2 tables.

**[00259]** Trial Design

**[00260]** Primary Study Endpoints/Secondary Endpoints

**[00261]** Primary Outcome Measures:

**[00262]** Severity of Disease (discharged, hospitalization, admission to intensive care unit [ICU], and death) [Baseline, Day 7, Day 14, Day 21, Day 28]

**[00263]** Study Design/Type

**[00264]** This study is a prospective cross-sectional observational study. The study will have 4 arms:

**[00265]** Arm 1: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length <24 (based on the CoADTS Test) and Tmprss2 SNP (rs8134378) positive (G)

**[00266]** Arm 2: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length  $\geq 24$  (based on the CoADTS Test) and Tmprss2 SNP (rs8134378) positive (G)

**[00267]** Arm 3: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length  $< 24$  (based on the CoADTS Test) and Tmprss2 SNP (rs8134378) negative (A)

**[00268]** Arm 4: Males first tested positive for SARS-CoV-2 at the site (hospital) with CAG length  $\geq 24$  (based on the CoADTS Test) and Tmprss2 SNP (rs8134378) negative (A)

**[00269]** Study Environment:

**[00270]** This is a multi-center study to be conducted in at least 2 countries – Spain and the US. This exact protocol will be followed in each country. There will be a minimum of 2 separate sites and 2 separate PIs. In the US, the study will be approved by an IRB and in the other countries by the appropriate Ethics Committees.

**[00271]** The study will be conducted at the site(s) listed above i.e., the PI's hospital. All data collection including sample collection will be performed at the site.

**[00272]** Study Design:

**[00273]** Study Phase Ia: Screening (first site visit)

**[00274]** The PI will screen each potential subject for the inclusion and exclusion criteria.

**[00275]** Study Phase Ib: Enrollment (first site visit)

**[00276]** Each qualified subject will complete and sign the informed consent form

**[00277]** Each subject will be assigned a subject study number

**[00278]** Study Phase Ic: Sample Collection (first site visit)

**[00279]** For each subject, the PI will collect the saliva DNA sample using the CoADTS Test Sample Collection Kit. The sample collection will be performed in accordance with IFU for the collection kit.

**[00280]** The sample collection kit will be sent to the hospital laboratory.

**[00281]** All information will be recorded in the appropriate CRFs.

**[00282]** Study Phase Id: Hospital Laboratory (first site visit)

**[00283]** The hospital laboratory will extract the DNA from the sample collection kit utilizing the DNA extraction kit provided with the CoADTS Test kit.

**[00284]** The laboratory will ship the extracted DNA to the CLIA laboratory

**[00285]** Study Phase II: Primary Outcome (Days: 0, 7, 14, 21, 28):

1. For each subject, the PI or PI assistant will record the subject's severity of disease
2. All information will be recorded in the appropriate CRFs

Inclusion Criteria

**[00286]** Male over the age of 18

**[00287]** First time present at the site

**[00288]** Laboratory confirmed SARS-CoV-2 infection

**[00289]** Able to give informed consent

#### Exclusion Criteria

**[00290]** Unable to give informed consent

**[00291]** Diagnosed with an additional respiratory co-infection

**[00292]** XXY males

#### Assessment of Efficacy

**[00293]** Efficacy Parameters

**[00294]** Severity of Disease

**[00295]** Clinical assessment of disease severity will be made by attending physician and reported to the PI or PI assistant. Disease severity will be categorized as: discharged, hospitalization, admission to intensive care unit [ICU] or and death.

#### Method and Timing

**[00296]** All assessments described in section 5.1 will be recorded on paper forms (CRFs) and stored with each subject's clinical study record.

[00297] The timing to complete the assessment of efficacy will be at Baseline, Day 7, Day 14, Day 21 and Day 28. After baseline assessment, the additional assessment can be performed by computerized hospital record search by the PI or PI assistant.

[00298] Example 16: A controlled study was conducted on 100 male patients with average age of 48.3 years old. Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. The treatment arm was prescribed bicalutamide (50 mg) once daily at the start of the trial, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis were defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C}$  /  $99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization was defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 was defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

[00299] All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 6 of 50 subjects in the bicalutamide arm were admitted to the hospital after their first visit. The average BCRSS score for the 6 admitted patients was 1.9. 17 of 50 subjects in the standard care group were admitted to the hospital with an average BCRSS score of 4.1.

[00300] Example 17: A controlled study was conducted on 40 male patients with average age of 41.6 years old. Patients were diagnosed with SARS-CoV-2 infection but were

showing relatively mild symptoms. Patients were divided into one of two arms. The treatment arm was prescribed darolutamide (300 mg) orally twice daily at the start of the trial, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis was defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization was defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 was defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00301]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 1 of 20 subjects in the darolutamide arm was admitted to the hospital after their first visit. The patient's BCRSS score was 2. 3 of 20 subjects in the standard care group were admitted to the hospital with an average BCRSS score of 3.6.

**[00302]** Example 18: A controlled study was conducted on 150 male patients with average age of 45.7 years old. Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. The treatment arm was prescribed abiraterone (500 mg) twice daily at the start of the trial, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis was defined as subject exhibiting symptoms of

acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization was defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 was defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00303]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 4 of 75 subjects in the abiraterone arm were admitted to the hospital after their first visit. The patients average BCRSS score was 1.8. 15 of 75 subjects in the standard care group were admitted to the hospital with an average BCRSS score of 4.7.

**[00304]** Example 19: A controlled study was conducted on 90 male patients with average age of 51 years old. Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. The treatment arm was prescribed nilutamide (300 mg) orally once daily at the start of the trial, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis was defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization was defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00305]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 3 of 50 subjects in the nilutamide arm were admitted to the hospital after their first visit. The patients BCRSS score was 1.3. 8 of 40 subjects in the standard care group were admitted to the hospital with an average BCRSS score of 4.0.

**[00306]** Example 20: A controlled study was conducted on 16 male patients with average age of 64 years old. Patients were diagnosed with SARS-CoV-2 infection but were showing relatively mild symptoms. Patients were divided into one of two arms. The treatment arm received docetaxel 75 mg/m<sup>2</sup> IV over 1 hour at the start of the trial, the control arm received standard care. Patients were instructed to go home but return to the hospital if symptoms became worse. Efficacy parameters were defined as 1.) COVID-19 Diagnosis: COVID-19 positive diagnosis was defined as subject exhibiting symptoms of acute respiratory infection, defined as one or more of the following cough, fever ( $> 37.5^{\circ} \text{C} / 99.5^{\circ} \text{F}$ ), shortness of breath, sore throat, and a positive SARS-CoV-2 rtPCR test 2.) COVID-19 Hospitalization defined as confirmed hospitalization due to COVID-19, and 3.) Symptoms Severity of COVID-19 was defined as symptoms severity of COVID-19 using Brescia-COVID Respiratory Severity Scale (BCRSS).

**[00307]** All subjects were tested and found to be positive for SARS-CoV-2 infection. All subjects were monitored for one month after the initiation of the therapy. 0 of 8 subjects in the docetaxel arm were admitted to the hospital after their first visit. 2 of 8 subjects in the standard care group were admitted to the hospital with an average BCRSS score of 4.5.

[00308] It should be noted that the dosage used in administering embodiments of the compositions can be low and still be effective. A low dosage can be within a range from 1/10x to 1x of the following exemplary dosages listed:

topical skin application of finasteride at 10% (w/w)

oral finasteride at 0.1-10 mg

dutasteride at 0.1 mg/day to 1.0 mg/day

degarelix at 240 mg

oral cannabidiol at 10/mg/Kg/day

oral flutamide at 750 mg/day

enzalutamide at 160 mg qd

oral dutasteride at 0.25 mg/day

apalutamide at 60 mg 4 times per day

injection of cyproterone acetate (300 mg).

subcutaneous injection of degarelix (120 mg)

bicalutamide at 50 mg per day

subcutaneous injection of degarelix (120 mg)

oral darolutamide at 300 mg twice daily

abiraterone at 500 mg twice daily

oral nilutamide at 300 mg once daily

docetaxel at 75 mg/m<sup>2</sup> IV over 1 hour

[00309] However, dosages within a range from 1/10x to 3x of the above identified dosages can be used. Thus, dosages can be within a range from:

topical skin application of finasteride at 1-30% (w/w)

oral finasteride at 0.01-30 mg  
dutasteride at 0.1 mg/day to 3.0 mg/day  
degarelix at 24 mg-720 mg  
oral cannabidiol at 1-30/mg/Kg/day  
oral flutamide at 75-2,250 mg/day  
enzalutamide at 16-480 mg qd  
oral dutasteride at 0.025-0.75 mg/day  
apalutamide at 6-180 mg 4 times per day  
injection of cyproterone acetate (30-900 mg).  
subcutaneous injection of degarelix (12-360 mg)  
bicalutamide at 5-150 mg per day  
subcutaneous injection of degarelix (12-360 mg)  
oral darolutamide at 30-900 mg twice daily  
abiraterone at 50-1500 mg twice daily  
oral nilutamide at 30-900 mg once daily  
docetaxel at 7.5-225 mg/m<sup>2</sup> IV over 1 hour

## CLAIMS

1. A composition for treatment of a viral respiratory infection, the composition comprising any one or a combination of an anti-androgen or an androgen receptor antagonist.

2. The composition of claim 1, wherein:

the anti-androgen is any one or combination of: cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, medrogestone, oxendolone, osaterone, bifluranol, finasteride, dutasteride, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medrogestone, nomegestrol acetate, promegestone, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide, epristeride, alfaestradiol, isotretinoin, saw palmetto, darolutamide, galeterone, proxalutamide, triptorelin pamoate, allylestrenol, chlormadinone acetate, or degarelix.

3. The composition of claim 1, wherein the composition is formulated to facilitate administration of the composition topically to the skin, nasally, sub-lingually, orally, by injection, via inhalation, or ocular application.

4. The composition of claim 1, wherein the viral respiratory infection is any one or combination of coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV, or rhinoviruses.

5. The composition of claim 1, wherein the composition is formulated for use as a treatment of the viral respiratory infection, a therapy for the viral respiratory infection, a

prophylactic for the viral respiratory infection, and/or a preventive measure for contracting the viral respiratory infection.

6. The composition of claim 5, wherein the composition is further formulated for use as a treatment for prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer and/or benign prostatic hyperplasia.

7. A method of treating a patient having or suspected of having a viral respiratory infection, the method comprising:

administering a composition to the patient, the composition including any one or combination of an anti-androgen or an androgen receptor antagonist.

8. The method of claim 7, wherein:

the anti-androgen is any one or combination of: cyproterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, medrogestone, oxendolone, osaterone, bifluranol, finasteride, dutasteride, flutamide, bicalutamide, nilutamide, topilutamide, enzalutamide, apalutamide, dienogest, drospirenone, medrogestone, nomegestrol acetate, promegestone, trimegestone, ketoconazole, abiraterone acetate, seviteronel, aminoglutethimide, epristeride, alfaestradiol, isotretinoin, saw palmetto, darolutamide, galeterone, proxalutamide, triptorelin pamoate, allylestrenol, chlormadinone acetate, or degarelix.

9. The method of claim 7, wherein the administration of the composition involves any one or combination of topical application to the skin, nasal application, sublingual application, oral application, via injection, via inhalation, or ocular application.

10. The method of claim 7, wherein the viral respiratory infection is any one or combination of coronavirus, influenza, influenza A, influenza B, SARS-CoV-1, SARS-CoV-2, MERS-CoV or rhinoviruses.

11. The method of claim 7, wherein the composition is used as a treatment for the viral respiratory infection, a therapy for the viral respiratory infection, a prophylactic for the viral respiratory infection, and/or a preventive measure for contracting the viral respiratory infection.

12. The method of claim 7, wherein the treatment involves administering the composition as a treatment for the viral respiratory infection and/or a prophylactic for the viral respiratory infection before, during, and/or after the patient is first diagnosed with the viral respiratory infection and/or before, during, and/or after the patient is hospitalized due to the viral respiratory infection.

13. The method of claim 11, wherein the composition is further used as a treatment for prostate cancer, castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer and/or benign prostatic hyperplasia.

14. The method of claim 7, wherein administering the composition involves administering:

topical skin application of finasteride at 1-30% (w/w), oral finasteride at 0.01-30 mg, dutasteride at 0.1 mg/day to 3.0 mg/day, degarelix at 24 mg-720 mg, oral flutamide at 75-2,250 mg/day, enzalutamide at 16-480 mg qd, oral dutasteride at 0.025-0.75 mg/day, apalutamide at 6-180 mg 4 times per day, injection of 30-900 mg of cyproterone acetate, subcutaneous injection of 12-360 mg of degarelix, bicalutamide at 5-150 mg per day, subcutaneous injection of 12-360 mg of degarelix, oral darolutamide at 30-900 mg twice daily, abiraterone at 50-1500 mg twice daily, oral nilutamide at 30-900 mg once daily, or docetaxel at 7.5-225 mg/m<sup>2</sup> IV over 1 hour.

15. The method of claim 7, wherein administering the composition involves administering:

topical skin application of finasteride at 1-10% (w/w), oral finasteride at 0.1-10 mg, dutasteride at 0.1 mg/day to 1.0 mg/day, degarelix at 24 mg-240 mg, oral flutamide at 75-750 mg/day, enzalutamide at 16-160 mg qd, oral dutasteride at 0.025-0.25 mg/day, apalutamide at 6-60 mg 4 times per day, injection of 30-300 mg of cyproterone acetate, subcutaneous injection of 12-120 mg of degarelix, bicalutamide at 5-50 mg per day, subcutaneous injection of 12-120 mg of degarelix, oral darolutamide at 30-300 mg twice daily, abiraterone at 50-500 mg twice daily, oral nilutamide at 30-300 mg once daily, or docetaxel at 7.5-750 mg/m<sup>2</sup> IV over 1 hour.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2021/019201

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>					
INV.	A61K31/00	A61K31/167	A61K31/203	A61K31/451	A61K31/473
	A61K31/496	A61K31/565	A61K31/57	A61K31/575	A61K31/585
	A61P11/00	A61P31/12	A61P31/16	A61K9/00	A61K31/277

According to International Patent Classification (IPC) or to both national classification and IPC

<b>B. FIELDS SEARCHED</b>
Minimum documentation searched (classification system followed by classification symbols) A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data
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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ON BEHALF OF THE HONG KONG HOSPITAL AUTHORITY SARS COLLABORATIVE GROUP (HASCOG) YIN-CHUN YAM ET AL: "Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong", JOURNAL OF INFECTION, ACADEMIC PRESS, LONDON, GB, vol. 54, no. 1, 22 December 2006 (2006-12-22), pages 28-39, XP005750857, ISSN: 0163-4453	1-15
Y	abstract ----- -/--	1-15

Further documents are listed in the continuation of Box C.       See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  1 June 2021	Date of mailing of the international search report  11/06/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Strack, Eberhard
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2021/019201

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NIELSEN HEBER C. ET AL:            "Dihydrotestosterone Inhibits Fetal Rabbit            Pulmonary Surfactant Production",            THE JOURNAL OF CLINICAL INVESTIGATION,            vol. 69, no. 3, 1 March 1982 (1982-03-01),            pages 611-616, XP55809434,            GB            ISSN: 0021-9738, DOI: 10.1172/JCI110488            abstract            Introduction</p> <p style="text-align: center;">-----</p>	1-15
A,P	<p>GOREN ANDY ET AL: "A preliminary            observation: Male pattern hair loss among            hospitalized COVID-19 patients in Spain -            A potential clue to the role of androgens            in COVID-19 severity",            JOURNAL OF COSMETIC DERMATOLOGY,            vol. 19, no. 7, 23 April 2020 (2020-04-23)            , pages 1545-1547, XP55809437,            GB            ISSN: 1473-2130, DOI: 10.1111/jocd.13443            Retrieved from the Internet:            URL:https://onlinelibrary.wiley.com/doi/fu            11-xml/10.1111/jocd.13443&gt;            abstract</p> <p style="text-align: center;">-----</p>	1-15