

CLAIMS

1. A method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method comprising performing a genetic risk
5 assessment of the human subject, wherein the genetic risk assessment involves detecting, in a biological sample derived from the human subject, the presence at least two polymorphisms associated with a severe response to a Coronavirus infection.
2. The method of claim 1 which comprises detecting the presence of at least three,
10 at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 100, at least 120, at least 140, at least 160, at least 180, at least 200, at least 250, at least 300 or at least 306 polymorphisms associated with a severe response to a Coronavirus infection.
- 15 3. The method of claim 1 or claim 2, wherein the polymorphisms are selected from in any one of Tables 1 to 6, 8, 19 or 22 or a polymorphism in linkage disequilibrium with one or more thereof.
- 20 4. The method according to any one of claims 1 to 3 which at least comprises detecting polymorphisms at one or more or all of rs10755709, rs112317747, rs112641600, rs118072448, rs2034831, rs7027911 and rs71481792, or a polymorphism in linkage disequilibrium with one or more thereof.
- 25 5. The method according to any one of claims 1 to 3 which at least comprises detecting polymorphisms at one or more or all of rs10755709, rs112317747, rs112641600, rs115492982, rs118072448, rs1984162, rs2034831, rs7027911 and rs71481792, or a polymorphism in linkage disequilibrium with one or more thereof.
- 30 6. The method of claim 1 or claim 2, wherein the polymorphisms are selected from Table 1 and/or Table 6 or a polymorphism in linkage disequilibrium with one or more thereof.
7. The method of claim 1 or claim 2, wherein the polymorphisms are selected from
35 Table 4 or a polymorphism in linkage disequilibrium with one or more thereof.

8. The method of claim 7, wherein the method comprises, or consists of, detecting the presence of at least 60, or each, of the polymorphisms provided in Table 4 or a polymorphism in linkage disequilibrium with one or more thereof.
- 5 9. The method of claim 1 or claim 2, wherein the polymorphisms are selected from Table 2 or a polymorphism in linkage disequilibrium with one or more thereof.
10. The method of claim 1 or claim 2, wherein the polymorphisms are selected from Table 3 and/or Table 8 or a polymorphism in linkage disequilibrium with one or more
10 thereof.
11. The method of claim 1 or claim 2, wherein the polymorphisms are selected from Table 3 or a polymorphism in linkage disequilibrium with one or more thereof.
- 15 12. The method of claim 11 which comprises detecting the presence of each of the polymorphisms provided in Table 3 or a polymorphism in linkage disequilibrium with one or more thereof.
13. The method according to any one of claims 1 to 12 which further comprises
20 performing a clinical risk assessment of the human subject; and
combining the clinical risk assessment and the genetic risk assessment to obtain the risk of a human subject developing a severe response to a Coronavirus infection.
14. The method of claim 13, wherein the clinical risk assessment includes obtaining
25 information from the subject on one or more or all of: age, gender, race/ethnicity, blood type, height, weight, does the human have or has had an cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had diabetes, does the human have or has had an haematological cancer, does the human have or has had hypertension, does the human have or has had an immunocompromised
30 disease, does the human have or has had an haematological cancer, does the human have or has had liver disease, does the human have or has had an non-haematological cancer, does the human have or has had a respiratory disease (other than asthma), and does the human have or has had an autoimmune disease.

15. The method according to any one of claims 1 to 14, wherein combining the clinical risk assessment and the genetic risk assessment comprises adding or multiplying the risk assessments.
- 5 16. A method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method comprising detecting, in a biological sample derived from the human subject, the presence of a polymorphism provided in any one of Tables 1 to 6, 8, 19 or 22, or a polymorphism in linkage disequilibrium therewith.
- 10 17. The method of claim 16, wherein the polymorphism is provided in Table 19 and/or 22 or is a polymorphism in linkage disequilibrium therewith.
18. The method of claim 16, wherein the polymorphism is provided in Table 3, Table 6, is rs2274122, is rs1868132, is rs11729561, is rs1984162, is rs8105499 or is a
15 polymorphism in linkage disequilibrium therewith.
19. The method of claim 146 wherein the polymorphism is provided in Table 3, is rs2274122, is rs1868132, is rs11729561, is rs1984162, is rs8105499 or is a polymorphism in linkage disequilibrium therewith.
- 20 20. A method of determining the identity of the alleles of fewer than 100,000 polymorphisms in a human subject selected from the group of subjects consisting of humans in need of assessment for the risk of developing a severe response to a Coronavirus infection to produce a polymorphic profile of the subject, comprising
- 25 (i) selecting for allelic identity analysis at least two polymorphisms provided in any one of Tables 1 to 6, 8, 19 or 22, or a polymorphism in linkage disequilibrium with one or more thereof,
- (ii) detecting, in a biological sample derived from the human subject, the polymorphisms, and
- 30 (iii) producing the polymorphic profile of the subject screening based on the identity of the alleles analysed in step (ii), wherein fewer than 100,000 polymorphisms are selected for allelic identity analysis in step (i) and the same fewer than 100,000 polymorphisms are analysed in step (ii).
- 35 21. The method according to any one of claims 1 to 20, wherein the polymorphism(s) in linkage disequilibrium has a linkage disequilibrium above 0.9.

22. The method according to any one of claims 1 to 21, wherein the polymorphism(s) in linkage disequilibrium has a linkage disequilibrium of 1.

5 23. A method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method comprising performing a clinical risk assessment of the human subject, wherein the clinical risk assessment comprises obtaining information from the subject on two, three, four, five or more or all of age, gender, race/ethnicity, height, weight, blood type, does the human have or has had an
10 cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had an autoimmune disease, does the human have or has had an haematological cancer, does the human have or has had an immunocompromised disease, does the human have or has had an non-haematological cancer, does the human have or has had diabetes, does the human have or has had liver disease, does the human
15 have or has had hypertension and does the human have or has had a respiratory disease (other than asthma).

24. The method of claim 23 which comprises obtaining information from the subject on age and gender.

20

25. The method of claim 23 which comprises obtaining information from the subject on age, gender, race/ethnicity, height, weight, does the human have or has had an cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had diabetes, does the human have or has had an haematological
25 cancer, does the human have or has had hypertension, does the human have or has had an non-haematological cancer, and does the human have or has had a respiratory disease (other than asthma).

26. The method of claim 23 which comprises obtaining information from the subject on age, gender, race/ethnicity, blood type, height, weight, does the human have or has
30 had an cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had diabetes, does the human have or has had an haematological cancer, does the human have or has had hypertension, does the human have or has had an immunocompromised disease, does the human have or has had an
35 haematological cancer, does the human have or has had liver disease, does the human

have or has had an non-haematological cancer, and does the human have or has had a respiratory disease (other than asthma).

27. A method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method comprising

- i) performing a genetic risk assessment of the human subject, wherein the genetic risk assessment involves detecting, in a biological sample derived from the human subject, polymorphisms at rs10755709, rs112317747, rs112641600, rs118072448, rs2034831, rs7027911 and rs71481792,
- 10 ii) performing a clinical risk assessment of the human subject, wherein the clinical risk assessment comprises obtaining information from the subject on age, gender, race/ethnicity, height, weight, does the human have or has had an cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had diabetes, does the human have or has had an haematological
- 15 cancer, does the human have or has had hypertension, does the human have or has had an non-haematological cancer, and does the human have or has had a respiratory disease (other than asthma), and
- iii) combining the genetic risk assessment with the clinical risk assessment to determine the risk of a human subject developing a severe response to a Coronavirus
- 20 infection.

28. The method of claim 27, wherein

- a) a β coefficient of 0.124239 is assigned for each G allele at rs10755709;
- b) a β coefficient of 0.2737487 is assigned for each C allele at rs112317747;
- 25 c) a β coefficient of -0.2362513 is assigned for each T allele at rs112641600;
- d) a β coefficient of -0.1995879 is assigned for each C allele at rs118072448;
- e) a β coefficient of 0.2371955 is assigned for each C allele at rs2034831;
- f) a β coefficient of 0.1019074 is assigned for each A allele at rs7027911; and
- g) a β coefficient of -0.1058025 is assigned for each T allele at rs71481792.

30

29. The method of claim 27 or claim 28, wherein the subject is between 50 and 84 years of age and

- a) a β coefficient of 0.5747727 is assigned if the subject is between 70 and 74 years of age;
- 35 b) a β coefficient of 0.8243711 is assigned if the subject is between 75 and 79 years of age;

c) a β coefficient of 1.013973 is assigned if the subject is between 80 and 84 years of age;

d) a β coefficient of 0.2444891 is assigned if the subject is male;

e) a β coefficient of 0.29311 is assigned if the subject is an ethnicity other than

5 Caucasian;

f) the subjects height (in metres (m)) and weight (in kilograms (kg)) is applied to the formula: (10 times m^2) divided by kg, which is multiplied by -1.602056 to provide the β coefficient to be assigned;

10 g) a β coefficient of 0.4041337 is assigned if the subject has ever been diagnosed as having a cerebrovascular disease;

h) a β coefficient of 0.6938494 is assigned if the subject has ever been diagnosed as having a chronic kidney disease;

i) a β coefficient of 0.4297612 is assigned if the subject has ever been diagnosed as having diabetes;

15 j) a β coefficient of 1.003877 is assigned if the subject has ever been diagnosed as having haematological cancer;

k) a β coefficient of 0.2922307 is assigned if the subject has ever been diagnosed as having hypertension;

20 l) a β coefficient of 0.2558464 is assigned if the subject has ever been diagnosed as having a non-haematological cancer; and

m) a β coefficient of 1.173753 is assigned if the subject has ever been diagnosed as having a respiratory disease (other than asthma).

30. The method of claim 27 or claim 28, wherein the subject is between 18 and 84 years of age and

a) a β coefficient of -1.3111 is assigned if the subject is between 18 and 29 years of age;

b) a β coefficient of -0.8348 is assigned if the subject is between 30 and 39 years of age;

30 c) a β coefficient of -0.4038 is assigned if the subject is between 40 and 49 years of age;

d) a β coefficient of 0.5747727 is assigned if the subject is between 70 and 74 years of age;

35 e) a β coefficient of 0.8243711 is assigned if the subject is between 75 and 79 years of age;

f) a β coefficient of 1.013973 is assigned if the subject is between 80 and 84 years of age;

g) a β coefficient of 0.2444891 is assigned if the subject is male;

h) a β coefficient of 0.29311 is assigned if the subject is an ethnicity other than

5 Caucasian;

i) the subjects height (in metres (m)) and weight (in kilograms (kg)) is applied to the formula: (10 times m^2) divided by kg, which is multiplied by -1.602056 to provide the β coefficient to be assigned;

j) a β coefficient of 0.4041337 is assigned if the subject has ever been diagnosed
10 as having a cerebrovascular disease;

k) a β coefficient of 0.6938494 is assigned if the subject has ever been diagnosed as having a chronic kidney disease;

l) a β coefficient of 0.4297612 is assigned if the subject has ever been diagnosed as having diabetes;

m) a β coefficient of 1.003877 is assigned if the subject has ever been diagnosed as having haematological cancer;

n) a β coefficient of 0.2922307 is assigned if the subject has ever been diagnosed as having hypertension;

o) a β coefficient of 0.2558464 is assigned if the subject has ever been
20 diagnosed as having a non-haematological cancer; and

p) a β coefficient of 1.173753 is assigned if the subject has ever been diagnosed as having a respiratory disease (other than asthma).

31. The method according to any one of claims 27 to 30, wherein in step iii) the
25 genetic risk assessment is combined with the clinical risk assessment using the following formula:

Long Odds (LO) = $-1.36523 + \text{SRF} + \sum \text{Clinical } \beta \text{ coefficients}$,

and wherein SRF is the SNP Risk Factor which is determined using the following formula:

30 $\sum (\text{No of Risk Alleles} \times \text{SNP } \beta \text{ coefficient})$.

32. A method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method comprising

i) performing a genetic risk assessment of the human subject, wherein the
35 genetic risk assessment involves detecting, in a biological sample derived from the

human subject, polymorphisms at rs10755709, rs112317747, rs112641600, rs115492982, rs118072448, rs1984162, rs2034831, rs7027911 and rs71481792,

ii) performing a clinical risk assessment of the human subject, wherein the clinical risk assessment comprises obtaining information from the subject of age, gender, race/ethnicity, blood type, height, weight, does the human have or has had an cerebrovascular disease, does the human have or has had a chronic kidney disease, does the human have or has had diabetes, does the human have or has had an haematological cancer, does the human have or has had hypertension, does the human have or has had an immunocompromised disease, does the human have or has had an haematological cancer, does the human have or has had liver disease, does the human have or has had an non-haematological cancer, and does the human have or has had a respiratory disease (other than asthma), and

iii) combining the genetic risk assessment with the clinical risk assessment to determine the risk of a human subject developing a severe response to a Coronavirus infection.

33. The method of claim 32, wherein

- a) a β coefficient of 0.1231766 is assigned for each G allele at rs10755709;
- b) a β coefficient of 0.2576692 is assigned for each C allele at rs112317747;
- c) a β coefficient of -0.2384001 is assigned for each T allele at rs112641600;
- d) a β coefficient of -0.1965609 is assigned for each C allele at rs118072448;
- e) a β coefficient of 0.2414792 is assigned for each C allele at rs2034831;
- f) a β coefficient of 0.0998459 is assigned for each A allele at rs7027911;
- g) a β coefficient of -0.1032044 is assigned for each T allele at rs71481792;
- h) a β coefficient of 0.4163575 is assigned for each A allele at rs115492982; and
- i) a β coefficient of 0.1034362 is assigned for each A allele at rs1984162.

34. The method of claim 32 or claim 33, wherein the subject is between 50 and 84 years of age and

- a) a β coefficient of 0.1677566 is assigned if the subject is between 65 and 69 years of age;
- b) a β coefficient of 0.6352682 is assigned if the subject is between 70 and 74 years of age;
- c) a β coefficient of 0.8940548 is assigned if the subject is between 75 and 79 years of age;

d) a β coefficient of 1.082477 is assigned if the subject is between 80 and 84 years of age;

e) a β coefficient of 0.2418454 is assigned if the subject is male;

f) a β coefficient of 0.2967777 is assigned if the subject is an ethnicity other than Caucasian;

g) the subjects height (in metres (m)) and weight (in kilograms (kg)) is applied to the formula: (10 times m^2) divided by kg, which is multiplied by -1.560943 to provide the β coefficient to be assigned;

h) a β coefficient of 0.3950113 is assigned if the subject has ever been diagnosed as having a cerebrovascular disease;

i) a β coefficient of 0.6650257 is assigned if the subject has ever been diagnosed as having a chronic kidney disease;

j) a β coefficient of 0.4126633 is assigned if the subject has ever been diagnosed as having diabetes;

k) a β coefficient of 1.001079 is assigned if the subject has ever been diagnosed as having haematological cancer;

l) a β coefficient of 0.2640989 is assigned if the subject has ever been diagnosed as having hypertension;

m) a β coefficient of 0.2381579 is assigned if the subject has ever been diagnosed as having a non-haematological cancer;

n) a β coefficient of 1.148496 is assigned if the subject has ever been diagnosed as having a respiratory disease (other than asthma);

o) a β coefficient of -0.229737 is assigned if the subject has an ABO blood type;

p) a β coefficient of 0.6033541 is assigned if the subject has ever been diagnosed as having an immunocompromised disease;

q) a β coefficient of 0.2301902 is assigned if the subject has ever been diagnosed as having liver disease.

35. The method according to any one of claims 32 to 34, wherein in step iii) the genetic risk assessment is combined with the clinical risk assessment using the following formula:

$$\text{Long Odds (LO)} = 1.469939 + \text{SRF} + \sum \text{Clinical } \beta \text{ coefficients,}$$

and wherein SRF is the SNP Risk Factor which is determined using the following formula:

$$\sum (\text{No of Risk Alleles} \times \text{SNP } \beta \text{ coefficient}).$$

36. The method according to any one of claims 27 to 35 which further comprises determining the probability the subject would require hospitalisation if infected with a Coronavirus using the following formula:

$$e^{LO}/(1+e^{LO}),$$

5 which is then multiplied by 100 to obtain a percent chance of hospitalisation being required.

37. The method according to any one of claims 1 to 36, wherein the risk assessment produces a score and the method further comprises comparing the score to a
10 predetermined threshold, wherein if the score is at, or above, the threshold the subject is assessed at being at risk of developing a severe response to a Coronavirus infection.

38. The method according to any one of claims 1 to 37, wherein the Coronavirus is a Betacoronavirus.

15

39. The method of claim 38, wherein the Coronavirus (Betacoronavirus) is Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), Severe acute respiratory syndrome-related coronavirus (SARS-CoV), Middle East respiratory syndrome-related coronavirus (MERS), Human coronavirus OC43 or Human
20 coronavirus HKU1.

40. The method of claim 38 or claim 39, wherein the Coronavirus (Betacoronavirus) is Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

25 41. A method for determining the need for routine diagnostic testing of a human subject for a Coronavirus infection comprising assessing the risk of the subject for developing a severe response to a Coronavirus infection using the method according to any one of claims 1 to 40.

30 42. A method of screening for a severe response to a Coronavirus infection in a human subject, the method comprising assessing the risk of the subject for developing a severe response to a Coronavirus infection using the method according to any one of claims 1 to 40, and routinely screening for a Coronavirus infection in the subject if they are assessed as having a risk for developing a severe response to a Coronavirus
35 infection.

43. The method of claim 41 or claim 42, wherein the screening involves analysing the subject for the virus or a symptom thereof.

44. A method for determining the need of a human subject for prophylactic anti-
5 Coronavirus therapy comprising assessing the risk of the subject for developing a severe response to a Coronavirus infection using the method according to any one of claims 1 to 40.

45. A method for preventing or reducing the risk of a severe response to a
10 Coronavirus infection in a human subject, the method comprising assessing the risk of the subject for developing a severe response to a Coronavirus infection using the method according to any one of claims 1 to 40, and if they are assessed as having a risk for developing a severe response to a Coronavirus infection
1) administering an anti-Coronavirus therapy and/or
15 2) isolating the subject.

46. An anti-Coronavirus infection therapy for use in preventing a severe response to a Coronavirus infection in a human subject at risk thereof, wherein the subject is assessed as having a risk for developing a severe response to a Coronavirus infection
20 using the method according to any one of claims 1 to 40.

47. The method according to any one of claims 44 to 46, wherein the therapy is selected from intubation to assist breathing, an anti-Coronavirus vaccine, convalescent plasma, chloroquine, hydroxychloroquine, Favipiravir, Remdesivir, Ivermectin,
25 Quercetin, Kaletra (lopinavir/ritonavir), Arbidol, Baricitinib, CM4620-IE, an IL-6 inhibitor, Tocilizumab and stem cells such as mesenchymal stem cells.

48. A method for stratifying a group of human subjects for a clinical trial of a candidate therapy, the method comprising assessing the individual risk of the subjects
30 for developing a severe response to a Coronavirus infection using the method according to any one of claims 1 to 40, and using the results of the assessment to select subjects more likely to be responsive to the therapy.

49. A kit comprising at least two sets of primers for amplifying two or more nucleic
35 acids, wherein the two or more nucleic acids comprise a polymorphism selected from

any one of Tables 1 to 6, 8, 19 or 22, or a single nucleotide polymorphism in linkage disequilibrium with one or more thereof.

50. A genetic array comprising at least two sets of probes for hybridising to two or
5 more nucleic acids, wherein the two or more nucleic acids comprise a polymorphism selected from any one of Tables 1 to 6, 8, 19 or 22, or a single nucleotide polymorphism in linkage disequilibrium with one or more thereof.

51. A computer implemented method for assessing the risk of a human subject
10 developing a severe response to a Coronavirus infection, the method operable in a computing system comprising a processor and a memory, the method comprising:

receiving genetic risk data for the human subject, wherein the genetic risk data was obtained by a method according to any one of claims 1 to 40;

processing the data to obtain the risk of a human subject developing a severe
15 response to a Coronavirus infection; and

outputting the risk of a human subject developing a severe response to a Coronavirus infection.

52. A computer implemented method for assessing the risk of a human subject
20 developing a severe response to a Coronavirus infection, the method operable in a computing system comprising a processor and a memory, the method comprising:

receiving clinical risk data and genetic risk data for the human subject, wherein the clinical risk data and genetic risk data were obtained by a method according to any one of claims 13 to 15 or 27 to 40;

25 processing the data to combine the clinical risk data with the genetic risk data to obtain the risk of a human subject developing a severe response to a Coronavirus infection; and

outputting the risk of a human subject developing a severe response to a Coronavirus infection.

30

53. A computer-implemented method for assessing the risk of a human subject developing a severe response to a Coronavirus infection, the method operable in a computing system comprising a processor and a memory, the method comprising:

receiving at least one clinical variable associated with the human subject,

35 wherein at least one clinical variable was obtained using a method according to any one of claims 20 to 26 or 36 to 40;

processing the data to obtain the risk of a human subject developing a severe response to a Coronavirus infection; and

outputting the risk of a human subject developing a severe response to a Coronavirus infection.

5

54. A system for assessing the risk of a human subject developing a severe response to a Coronavirus infection comprising:

system instructions for performing a genetic risk assessment of the human subject using the method according to any one of claims 1 to 40; and

10 system instructions to obtain the risk of a human subject developing a severe response to a Coronavirus infection.

55. A system for assessing the risk of a human subject developing a severe response to a Coronavirus infection comprising:

15 system instructions for performing a clinical risk assessment and a genetic risk assessment of the human subject using the method according to any one of claims 13 to 15 or 27 to 40; and

system instructions for combining the clinical risk assessment and the genetic risk assessment to obtain the risk of a human subject developing a severe response to a
20 Coronavirus infection.

56. A system for assessing the risk of a human subject developing a severe response to a Coronavirus infection comprising:

system instructions for performing a clinical risk assessment of the human
25 subject using the method according to any one of claims 20 to 26 or 36 to 40; and

system instructions to obtain the risk of a human subject developing a severe response to a Coronavirus infection.