

CLAIMS

Claim 1. A method of determining whether a tumour-specific mutation is likely to be clonal in a subject, the method comprising:

providing to a processor sequence data from one or more samples from the subject comprising tumour genetic material, the sequence data comprising for each of the one or more samples, at least two of: the number of reads in the sample that show the tumour-specific mutation (d_b), the number of reads in the sample that show the corresponding germline allele, and the total number of reads at the location of the tumour-specific mutation (d), and

determining, by the processor, the likelihood that the tumour-specific mutation is clonal as a posterior probability depending on:

a prior probability of the mutation being clonal, and

the probabilities of observing the sequence data if the tumour-specific mutation is (i) clonal and (ii) non-clonal, in view of a tumour fraction for each of the one or more samples and one or more candidate joint genotypes each comprising a genotype at the location of the tumour-specific mutation for a normal population, a reference tumour population that does not comprise the tumour-specific mutation and a variant tumour cell population that comprises the tumour-specific mutation.

Claim 2. The method of claim 1, wherein the probability of observing the sequence data in view of a tumour fraction in each sample and one or more candidate joint genotypes depends on the probability of observing the sequence data in view of a tumour fraction, cancer cell fraction and one or more candidate joint genotypes ($\Pr(d, d_b \mid \pi, \phi, t)$), optionally wherein the probability of observing the sequence data in view of a tumour fraction, cancer cell fraction and one or more candidate joint genotypes is a weighted sum of the probabilities of observing the sequence data in view of a tumour fraction, cancer cell fraction and each of the one or more candidate joint genotypes.

Claim 3. The method of claim 1 or claim 2, wherein the probability of observing the sequence data in view of a tumour fraction in each sample and one or more candidate joint genotypes is obtained as an integral over all possible values of the cancer cell fraction in each sample, wherein the cancer cell fraction is the proportion of tumour cells that comprise the tumour-specific mutation.

Claim 4. The method of any preceding claim, wherein sequence data from a plurality of samples is obtained and wherein the probability of observing the sequence data in view of a tumour fraction for each of the plurality of samples and one or more candidate joint genotypes is obtained as the product of the probability of observing the sequence data of each sample in

view of the tumour fraction in the respective sample and the one or more candidate joint genotypes.

Claim 5. The method of any preceding claim, further comprising obtaining, by the processor, for each sample, at least one estimate of the tumour fraction, and at least one corresponding set of one or more candidate joint genotypes.

Claim 6. The method of any preceding claim, wherein the probability of observing the sequence data combines a plurality of probabilities of observing the sequence data in view of a respective tumour fraction and a corresponding set of one or more candidate joint genotypes for at least one or the one or more samples, optionally wherein the method comprises obtaining, by the processor, for at least one or the one or more samples, a plurality of estimates of the tumour fraction, and a plurality of corresponding sets of one or more candidate joint genotypes.

Claim 7. The method of any preceding claim, wherein the prior probability of the mutation being clonal is set to a neutral prior, or to a value derived from prior data and/or expert knowledge.

Claim 8. The method of any preceding claim, further comprising repeating the method for a plurality of tumour-specific mutations identified in the subject, and optionally further comprising ranking or otherwise prioritising the plurality of tumour-specific mutations at least in part based on their determined likelihood of being clonal in the subject.

Claim 9. The method of any preceding claim, further comprising identifying, by the processor, one or more tumour-specific mutations in the subject, optionally using sequence data from one or more samples from the subject comprising tumour genetic material and one or more germline samples from the subject.

Claim 10. The method of any preceding claim, further comprising providing to a user, for example through a user interface, the determined probability of the tumour-specific mutation being clonal and/or a value derived therefrom or associated therewith.

Claim 11. A method of identifying one or more clonal neoantigens in a subject, the method comprising:

identifying a plurality of tumour-specific mutations in the subject;
determining whether one or more of the tumour-specific mutations is likely to be clonal in the subject using the method of any preceding claim; and
determining whether one or more of the tumour-specific mutations is likely to give rise to a neoantigen,
wherein a clonal neoantigen is a tumour-specific mutation that satisfies one or more predetermined criteria on whether the tumour-specific mutation is likely to be clonal and one or more criteria on whether the tumour-specific mutation is likely to give rise to a neoantigen.

Claim 12. The method of claim 11, wherein a clonal neoantigen is a tumor-specific mutation that satisfies at least a criterion selected from: having a probability of being clonal above a predetermined threshold, having a probability of being clonal that is above a threshold set adaptively to select a predetermined number of tumour-specific mutations with the highest probabilities of being clonal amongst the tumour-specific mutations for which a probability was determined, and having a probability of being clonal that is above a threshold set adaptively to select a predetermined top percentile of tumour-specific mutations amongst the tumour-specific mutations for which a probability was determined.

Claim 13. The method of claim 11 or claim 12, wherein a clonal neoantigen is a tumour-specific mutation that satisfies at least a criterion selected from: being associated with an expression product that is expressed in tumour cells, being predicted to result in a protein or peptide that is not expressed in the normal cells of the subject, being predicted to result in at least one peptide that is likely to be presented by an MHC molecule, preferably an MHC allele that is known to be present in the subject, and being predicted to result in a protein or peptide that is immunogenic.

Claim 14. A method of providing a prognosis for a subject that has been diagnosed as having cancer, the method comprising identifying a plurality of tumour-specific mutations in one or more samples from the subject and determining the likelihood of each of the tumour-specific mutations being clonal using the method of any of claims 1 to 9.

Claim 15. A method of providing an immunotherapy for a subject that has been diagnosed as having cancer, the method comprising:

identifying one or more clonal neoantigens using the method of any of claims 11 to 13; and

designing an immunotherapy that targets one or more of the clonal neoantigens identified.

Claim 16. The method of claim 15, wherein the immunotherapy that targets the one or more of the clonal neoantigens is an immunogenic composition, a composition comprising immune cells or a therapeutic antibody.

Claim 17. The method of claim 16, wherein the immunotherapy is a composition comprising T cells that recognise at least one of the one or more of the clonal neoantigens identified.

Claim 18. The method of claim 17, wherein said composition is enriched for T cells that target at least one of the one or more of the clonal neoantigens identified, optionally wherein the method comprises obtaining a population of T cells and expanding the population of T cells to increase

the number or relative proportion of T cells that target at least one of the one or more of the clonal neoantigens identified.

~~19. A composition comprising a population of T cells obtained or obtainable by the method according to claim 18.~~

5 ~~20. A method of treating a subject that has been diagnosed as having cancer, the method comprising administering an immunotherapy that has been provided using the method of claims 15 to 18, or the composition of claim 19.~~

Claim 2119. A system comprising:

a processor; and

10 a computer readable medium comprising instructions that, when executed by the processor, cause the processor to perform the steps of the method of any of claims 1 to 18.

Claim 2220. One or more non-transitory computer readable media comprising instructions that, when executed by one or more processors, cause the one or more processors to perform the steps of the method of any of claims 1 to 18.

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