

## CLAIMS

### WHAT IS CLAIMED IS:

1. A method of determining an individual's 4-digit human leukocyte antigen (HLA) allele composition, the method comprising:
  - a) mapping at least one nucleic acid sequence read from the individual to known HLA allele reference sequences to identify a first set of HLA alleles that explain the at least one nucleic acid sequence read; and
  - b) using a multiple sequence alignment (MSA) of known HLA allele reference sequences to identify one or more additional HLA allele reference sequences that match the at least one nucleic acid sequence read equally well as the first set of HLA alleles;wherein the individual's 4-digit HLA allele composition comprises the one or more additional HLA allele reference sequences that have the closest match to the at least one nucleic acid sequence read from the individual.
2. The method of claim 1, wherein nucleic acid sequence read is a DNA sequence read.
3. The method of claim 1, wherein the first set of HLA alleles comprise HLA alleles with at least 95% identity to the at least one nucleic acid sequence read from the individual.
4. The method of claim 3, wherein the one or more additional HLA allele reference sequences comprise HLA alleles with at least 95% identity to the at least one nucleic acid sequence read from the individual.
5. The method of claim 1, further comprising generating a solution set and a comparison set, wherein the solution set comprises the one or more additional HLA allele reference sequences that have the closest match to the at least one nucleic acid sequence read from the individual based upon core exons and the comparison set comprises HLA allele reference sequences that performed nearly as well those of the solution set.
6. The method of claim 5, wherein the core exons consist of exons 2 and 3 if the HLA allele reference sequence is a class I molecule.
7. The method of claim 5, wherein the core exons consist of exon 2 if the HLA allele reference sequence is a class II molecule.

8. The method of claim 1, further comprising comparing each of the HLA allele reference sequences of the solution set with one or more HLA allele reference sequences of the comparison set based upon all shared exons, wherein the solution set is updated with an HLA allele reference sequence from the comparison set if one or more of the HLA allele reference sequences from the comparison set better explains the nucleic acid sequence reads from the individual.
9. The method of claim 8, repeated until no HLA allele reference sequence from the solution set can be replaced by an HLA allele from the comparison set.
10. The method of claim 1, further comprising checking zygosity, wherein checking zygosity determines whether an individual is heterozygous or homozygous for any one or more HLA alleles of the individual's 4-digit HLA allele composition.
11. The method of claim 10, wherein checking zygosity comprises counting the at least one nucleic acid sequence read that maps to each allele of a given HLA gene.
12. The method of claim 11, wherein the individual is determined to be homozygous if the amount of sequence reads is at least 2 times or more than the next most strongly correlated allele.
13. The method of claim 1, further comprising determining a full resolution HLA composition, wherein determining the full resolution HLA composition comprises extracting the at least one nucleic acid sequence read that unambiguously align to an individual's 4-digit HLA allele composition and aligning the at least one nucleic acid sequence read to all HLA allele reference sequences that are contained within the 4-digit HLA allele group.
14. A method of determining an individual's 4-digit human leukocyte antigen (HLA) allele composition, the method comprising:
  - a) mapping at least one amino acid sequence translated from at least one nucleic acid sequence read from the individual to known HLA allele reference sequences to identify a first set of HLA alleles that explain the at least one amino acid sequence; and
  - b) using a multiple sequence alignment (MSA) of known HLA allele reference sequences to identify one or more additional HLA allele reference sequences that

match the at least one amino acid sequence equally well as the first set of HLA alleles;

wherein the individual's 4-digit HLA allele composition comprises the one or more additional HLA allele reference sequences that have the closest match to the at least one amino acid translated from at least one nucleic acid sequence read from the individual.

15. The method of claim 14, wherein nucleic acid sequence read is a DNA sequence read.
16. The method of claim 14, wherein the first set of HLA alleles comprise HLA alleles with at least 95% identity to the at least one amino acid sequence translated from at least one nucleic acid sequence read from the individual.
17. The method of claim 14, wherein the one or more additional HLA allele reference sequences comprise HLA alleles with at least 95% identity to the at least one amino acid sequence translated from at least one nucleic acid sequence read from the individual.
18. The method of claim 14, further comprising generating a solution set and a comparison set, wherein the solution set comprises the one or more additional HLA allele reference sequences that have the closest match to the at least at least one amino acid sequence based upon core exons and the comparison set comprises HLA allele reference sequences that performed nearly as well those of the solution set.
19. The method of claim 14, further comprising comparing each of the HLA allele reference sequences of the solution set with one or more HLA allele reference sequences of the comparison set based upon all shared exons, wherein the solution set is updated with an HLA allele reference sequence from the comparison set if one or more of the HLA allele reference sequences from the comparison set better explain the sequence data from the individual.
20. The method of claim 14, further comprising checking zygosity, wherein checking zygosity determines whether an individual is heterozygous or homozygous for any one or more HLA alleles of the individual's 4-digit HLA allele composition.