EXHIBIT F

2013 WL 7117636 (N.D.Cal.) (Trial Pleading)
United States District Court, N.D. California.
San Francisco Division

GENETIC TECHNOLOGIES LIMITED, an Australian corporation, Plaintiff,

v.

AGILENT TECHNOLOGIES, INC., a Delaware corporation, Defendant.

No. 3:12-cv-01616-RS.
December 5, 2013.

Courtroom: 3

Second Amended Complaint with Jury Demand

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Judge: Hon. Richard Seeborg.

Plaintiff Genetic Technologies Limited ("GTG") files this First Amended Complaint against Defendant Agilent Technologies, Inc. ("Agilent") alleging as follows:

I. *THE PARTIES*

1. Plaintiff GTG is an Australian corporation with a principal place of business in Victoria, Australia.

2. Upon information and belief, Agilent is a corporation organized and existing under the laws of the state of Delaware, with its principal place of business located at 5301 Stevens Creek Boulevard, Santa Clara, California 95051. Agilent can be served with process through its registered agent, The Corporation Trust Company, Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801.

II. *JURISDICTION AND VENUE*

3. This Court has exclusive jurisdiction of this action for patent infringement pursuant to 28 U.S.C. § 1338(a).

4. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

5. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400.

6. Upon information and belief, Agilent has minimum contacts with this judicial district such that this forum is a fair and reasonable one. Agilent has also each committed such purposeful acts and/or transactions in California that it reasonably

knew and/or expected that it could be hauled into court as a future consequence of such activity. Upon information and belief, Agilent has also transacted and/or, at the time of the filing of this Second Amended Complaint, is transacting business within the District of California. For these reasons, personal jurisdiction exists over Agilent and venue over this action is proper in this Court under 28 U.S.C. §§ 1391(b) and (c) and 28 U.S.C. § 1400(b).

III. *THE TECHNOLOGY*

7. This case involves technology related to deoxyribonucleic acid ("DNA") and in particular the non-coding regions of DNA. Genetic information for all living things is stored in DNA. Four bases, adenine (A), cytosine (C), guanine (G) and thymine (T), (also known as nucleotides) are the building blocks of DNA. In order to form the double helix structure of DNA, the nucleotides form pairs with each other - G pairs with C and T pairs with A.

8. DNA is replicated semi-conservatively via complementary strands according to basic Watson-Crick base pairing principles (A:T, G:C). Genes are the units of heredity and are stretches of the DNA of an organism that code for proteins or RNA molecules that have a function in the organism.

9. The DNA of different individuals shows significant variation, and some variations in the coding regions of genes are associated with particular traits or diseases. An allele of a gene is one particular genetic variation of the coding region of that gene. It is thus important to be able to determine genetic differences, sometimes referred to as polymorphism, between individuals, and in particular their allelic status. A particularly common form of polymorphism is single nucleotide polymorphism (SNP), but other forms of polymorphism e.g., insertions and deletions (small indels, as well as larger genomic deletions and duplications), also exist. Early efforts at determining genetic polymorphism therefore focused on directly analyzing the coding region of genes to detect certain alleles of interest.

10. In eukaryotes, sexual reproduction is often used to generate offspring with mixed genetic material from either parent. The majority of multicellular organisms are diploid for most of their lifespan - their cells have two copies of the genome and therefore two alleles of each gene. If both alleles of a particular gene are the same, the organism is homozygous at that genetic locus. If, on the other hand, the two alleles are different, the organism is heterozygous at that locus.

11. During the process of sexual reproduction, diploid organisms produce haploid gamete cells (sperm and eggs where the genome is in single copy) by meiosis, which fuse after mating to reproduce diploid cells. Chromosomal crossover by homologous recombination in diploid gamete precursors means that duplicate chromosomes exchange stretches of DNA during meiosis. The various haploid cells so-produced thus harbor shuffled chromosomes. Certain regions of each chromosome tend to be inherited together, with rare crossover or shuffling sometimes occurring. These stretches of DNA are said to be linked, or in linkage disequilibrium.

12. The term haplotype refers to the combination of alleles at adjacent loci that are inherited together. Thus haplotype defines a correlation between these alleles. Because of the common nature of SNPs, haplotype is also often taken to mean (the genotype of) a group of SNPs in linkage disequilibrium.

13. Eukaryotic DNA comprises the regions of genes and intergenic regions between genes, both of which can include interspersed repeat sequences and repeat DNA motifs. Genes include regions coding for protein and non-coding regions. By way of illustration, a representative polymorphic partial genomic DNA sequence is shown below which has been adapted from H. K. Tabor, N. J. Risch, R. M. Myers *Nature Reviews Genetics* 2002, *3*, 1-7.).

TABLE

The hypothetical promoter and partial gene shown above display single nucleotide polymorphism at four sites. SNPs 1 and 4 are in non-coding regions - SNP 1 in an intergenic region and SNP4 in the first intron - and SNPs 2 and 3 are in coding regions - both in the first exon. SNPs 2 and 3 contribute to phenotypic variation, and they are in linkage disequilibrium with SNPs 1 and 4 because a gene is a unit of inheritance, meaning that everything within the gene is linked and inherited as a block.

14. The earliest filing date for U.S. Patent No. 5,612,179 ("the '179 Patent") is August 25, 1989. The state of the art prior to August 25, 1989 can be appreciated from some of the literature of the time. Thus, for example, many molecular biology techniques were in use by 1989, such as the use of restriction endonucleases, cloning of genomic DNA, DNA sequencing, Southern blotting, and the use of probes in hybridisation assays. Restriction fragment length polymorphism was also used to directly investigate coding region polymorphism, protein sequencing using the Edman method and mass spectrometric sequencing was becoming an ever more useful tool. Enzyme-linked immunosorbent assays were then also used to detect polymorphism.

15. Prior to the filing of the application for the '179 Patent, the prevailing opinion was that non-coding DNA was simply debris - 'junk DNA' - which was abundant because of a steady accumulation over evolutionary history. Genetic variation in the 'junk DNA' was known, but was dismissed as irrelevant.

16. After years of research and substantial investment, the founders of GeneType AG proved that non-coding DNA is essential to the correct functioning of all cells. GeneType also showed that non-coding DNA variations may be linked to coding region alleles and that some variations in the non-coding regions may be used to detect diseases or traits that one associated with coding region variations. GeneType's discoveries enabled Dr. Malcolm Simons to invent and patent various methods by which polymorphisms found in the non-coding DNA of animals, humans and plants could be utilized to analyze coding region alleles of associated genes and to map gene traits of interest, including the '179 Patent.

17. By way of example, Dr. Simons discovered that polymorphisms in non-coding DNA regions can be in linkage disequilibrium with polymorphisms in coding regions of DNA, and thus that alleles can be detected by analyzing the sequence of the non-coding region. SNP 4 of the hypothetical partial genomic sequence shown above in paragraph 13 is in linkage disequilibrium with SNPs 2 and 3, and if SNP 1 is also in linkage disequilibrium, then the genotypes of SNPs 2 and 3 can be detected by determining the genotype of SNP1 or SNP4 as shown below.

TABLE

The genotypes of SNPs 1-4 are thus correlated, and SNPs 1 and 4 are *surrogate* markers for SNPs 2 and 3.

18. Before one can carry out the methods of the '179 Patent, the existence of the gene and the fact that it is polymorphic (multi-allelic) must be known, as does the sequence of the non-coding genomic DNA region. One also needs to have determined the fact that a non-coding polymorphism is serving as a surrogate marker for a desired physical characteristic, which is created by coding region DNA. The coding region allele or genotype produces a specific protein responsible for the phenotype which can be a disease trait or other desired characteristic.

19. Throughout a genome, numerous groups of SNPs in linkage disequilibrium also show non-coding/coding genotypic correlations, but the specific details of each correlation are different because of differences between genes and different numbers, relative locations and genotypes of SNPs. There are also many instances where no such non-coding/coding genotypic correlation exists and this emphasizes the need to determine the details in relevant situations.

20. Many genes are complex and there are often many haplotypes - an example of medium complexity chosen at random being the human *SLC12A3* gene, as shown below in a figure taken from N. Tanaka *et al. Diabetes* 2003, *52*, 2848-2853.

TABLE

The genotypic correlations between non-coding and coding polymorphisms are, as shown above, therefore not generic and cannot be described by a mathematical relationship.

21. Moreover, the correlation of non-coding DNA polymorphisms with coding region alleles is unlike Einstein's Law of Relativity, Archimedes' Principle of Buoyancy, or even the human body's metabolism of thiopurine drugs, all of which are generally applicable. Dissimilarly, linkage disequilibrium between non-coding and coding DNA is not ineluctable. Rather, any given linkage is specific to a particular region of the DNA of a group of individual organisms within a population of that species. Any given linkage is also not present in all species or even necessarily amongst other individuals of a particular species. Furthermore, any given linkage may not have existed in the past and may not exist in the future, as evolutionary inherency may transform the linkage. Finally, one non-coding polymorphism may indicate one, several or many haplotypes.

22. Despite this, the '179 Patent reveals the discovery that non-coding region polymorphisms can be used as surrogate markers for coding region polymorphisms on a case-by-case basis if the sequence of the non-coding region containing the polymorphism is known. The inventions of the '179 Patent are based on this discovery. However, it is limited only to very specific methods for the direct determination of the surrogate markers and the combination was not in use at the time of the invention of the '179 Patent.

23. Additionally, limitations recited in the claims of the '179 Patent were used in a novel way. Several claims of the '179 Patent require the use of a primer pair. A primer is an oligonucleotide, or short strand of nucleotides, which binds to a specific point on a DNA strand (“original strand”) to be amplified. The primer is a man-made tool used to amplify a portion of a DNA or RNA strand. The primer is a complementary nucleotide sequence strand (based on the Watson-Crick pairing) to the initial and/or end portions of the original strand to be copied. A DNA polymerase then adds the next complementary nucleotide to the end of the primer. Primer pairs have two primers, one used to replicate from the 3' end of the original strand and one to replicate from the (complement of the) 5' end of the original strand. Though primer pairs may indicate the use of polymerase chain reaction (PCR) for amplification, primers may be used in multiple applications to hybridize DNA.

24. Generally, when primer pairs are used in PCR amplification, the double helix structure of the original strand of DNA is denatured, so that the two original strands are separated. One primer attaches to the complementary sequence on one of the original strands and the second primer attaches to the complementary sequence on the other original strand. After a polymerase is added, nucleotides are added to one end of each primer to create a replicate copy of its respective strand. The original strands and the replicated strands are then again denatured. This time, primers attach to the complementary sequence on the 3' end of the original strand, the complementary sequence on the 5' end of the original strand, the complementary sequence on the 3' end of the replicated strand and the complementary sequence on the 5' end of the replicated strand. After the strands are again denatured, shorter replicated strands are created that only include the complementary sequence of the primers and the nucleotides between the primers. The denaturing, primer addition, and replication steps are repeated to amplify the copied DNA strands. There are many variations on the basic PCR technique, all of which result in amplification of the extracted genomic DNA. These replicated strands are synthetic and do not appear in nature in that form, as they may be only a portion of a DNA strand or fragmented and chemically different copies of the naturally occurring form.

25. The combinations recited in the claims of the '179 Patent were neither routine nor conventional at the time of the earliest filed application that resulted in the '179 Patent. PCR was known. However, no one had used a primer pair to amplify non-coding DNA to define a DNA sequence in genetic linkage with a coding region allele in order to detect that

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