IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENETIC TECHNOLOGIES LIMITED, a Australian corporation,	)	
Plaintiff,	)	Civil Action No. 1:12-CV-01738-LPS
v.	)	
HISTOGENETICS LLC, a Delaware limited liability company,	)	
Defendant.	)	

FIRST AMENDED COMPLAINT WITH JURY DEMAND

Plaintiff Genetic Technologies Limited ("GTG") for its First Amended Complaint against Defendant HistoGenetics LLC ("HistoGenetics"), alleges 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, HistoGenetics is a limited liability company organized and existing under the laws of the State of Delaware, with a place of business located at 300 Executive Blvd., Ossining, NY 10562. HistoGenetics can be served with process through its registered agent, National Registered Agents, Inc., 160 Greentree Drive, Suite 101, Dover, Delaware 19904.

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, HistoGenetics has minimum contacts with this judicial district such that this forum is a fair and reasonable one. HistoGenetics has also transacted and/or, at the time of the filing of this Complaint, is transacting business within the District of Delaware. Further, upon information and belief, HistoGenetics has committed acts of patent infringement complained of herein within the District of Delaware, including the offering for sale infringing DNA testing services. For these reasons, personal jurisdiction exists over HistoGenetics 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. The center of this dispute 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.

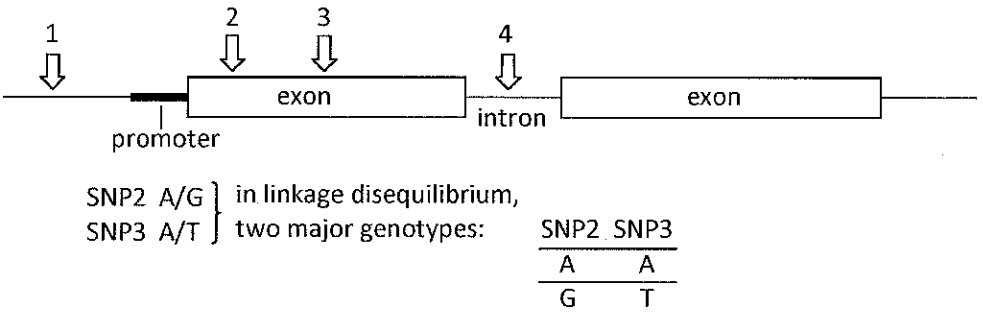
9. The DNA of different individuals shows significant variation, and some variations in the coding regions of genes are associated with particular traits or diseases. An allele of a gene is one particular genetic variation of the coding region of that gene. It is thus important to be able to determine 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 (indels), 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.).



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. 5,192,659 ("the '659 Patent") is August 25, 1989. The U.S. Patent Application that resulted in U.S. Patent No. 5,612,179 ("the '179 Patent") was a continuation application of the '659 Patent (the '659 Patent and the '179 Patent

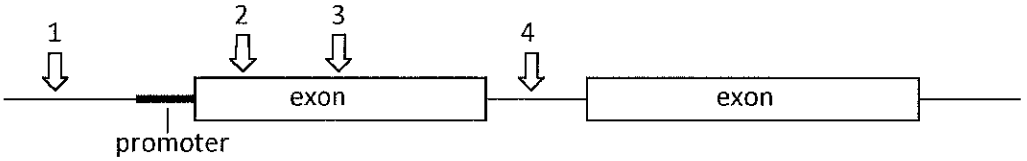
will herein collectively be referred to as "the Patents"). The state of the art prior to August 25, 1989 can be appreciated from some of the literature of the time. Thus, for example, many molecular biology techniques had become routine by 1989, such as the use of restriction endonucleases, cloning of genomic DNA, DNA sequencing, Southern blotting, and the use of probes in hybridisation assays. Restriction fragment length polymorphism was also in routine use to directly investigate coding region polymorphism, protein sequencing using the Edman method was routine 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 Patents, 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 Patents.

17. By way of example, Dr. Simons discovered that SNPs in non-coding DNA regions can be in linkage disequilibrium with SNPs 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.



SNP1 C/T Intergenic region
SNP2 A/G Coding region
SNP3 A/T Coding region
SNP4 T/G Deep intronic

in linkage disequilibrium, two major haplotypes:

SNP1	SNP2	SNP3	SNP4
C	A	A	T
T	G	T	G

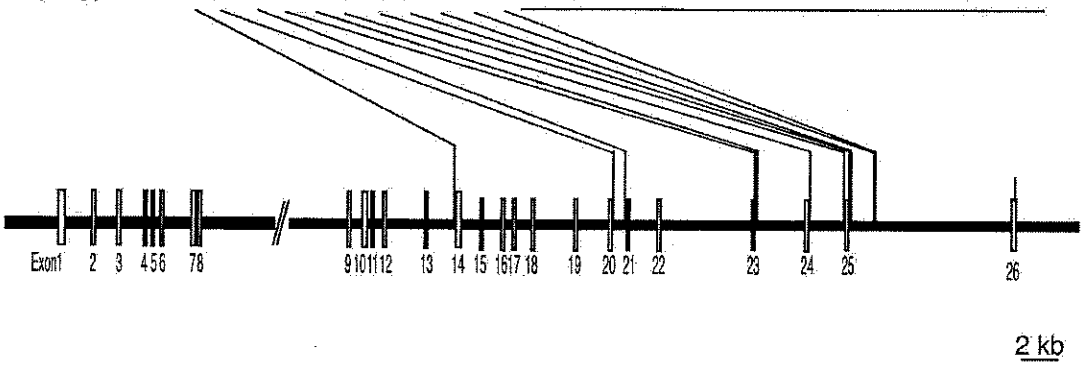
The genotypes of SNPs 1-4 are thus correlated, and SNPs 1 and 4 are *surrogate* markers for SNPs 2 and 3.

18. Before one can carry out the methods of the Patents, 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.

	*	Control	Case	χ^2	*p* value
haplotype 1	A G C G G T C G G C T	0.32	0.34	0.3	0.56
haplotype 2	G A T G G T C G G C T	0.15	0.16	0.1	0.75
haplotype 3	G G C G A C C G A C T	0.13	0.19	3.3	0.07
haplotype 4	G A T G G T C G G C C	0.1	0.08	0.4	0.54
haplotype 5	A A C G G T C G G C T	0.09	0.1	0.1	0.73
haplotype 6	G G T G A C C G A C T	0.06	0.06	0.01	0.92
haplotype 7	G G C A A T T A G T T	0.04	0.006	9.0	0.0027
haplotype 8	G A C G G T C A A C T	0.02	0.02	0.001	0.97
haplotype 9	G A C A A T T A G T T	0.02	0.003	4.4	0.03
haplotype 10	G A C G A T C A A C T	0.02	0.02	0.001	0.97



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 Patents reveal 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 Patents 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 Patents.

23. Additionally, limitations recited in the claims of the Patents were used in a novel way. Several claims of the '179 Patent and all of the claims of the '659 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 DNA strand and one to replicate from the (complement of the) 5' end of the original DNA strand. Though primer pairs 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, 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. These replicated strands are synthetic and do not appear in nature, as they are only a portion of a DNA strand.

25. The combinations recited in the claims of the Patents were neither routine nor conventional at the time of the earliest filed application that resulted in the Patents. 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 allele. Furthermore, amplification was not inherent or necessary to utilizing the correlation between the polymorphism in the non-coding region and the polymorphism in the coding region.

26. One claimed method of the '179 Patent – Claim 1 – involves the detection of at least one coding region allele of a multi-allelic genetic locus by amplifying a region of non-coding DNA with a primer pair, and then analyzing the amplified sequence to detect the allele.

Claim 1 first requires "amplif[ication of] genomic DNA with a primer pair that spans a non-coding region sequence." Second, the primer pair has to define "a DNA sequence which is in genetic linkage with said genetic locus and contain a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele." Third, "the amplified DNA sequence [must be analyzed] to detect the allele." Claim 1 of the '179 Patent thus does not simply describe a law of nature or natural phenomenon. Rather, it describes very specific steps for exploiting the discovery that "intron sequences that exhibit linkage disequilibrium with adjacent and remote loci can be used to detect alleles of those loci."

27. Claim 1 of the '179 Patent and Claim 1 of the '659 Patent require amplification of genomic DNA with a primer pair. The process of amplification requires a machine (for example a PCR machine) and transforms regions of native genomic DNA extracted from an organism into synthetic DNA fragments using a pair of synthetic oligonucleotide primers. The DNA of most species is methylated at the 5'-position of a fraction of cytosines across the genome. This methylation affects the function of the DNA, e.g. gene expression, and provides additional epigenetic regulation needed to govern the development of multiple cell types. When genomic DNA is amplified with a primer pair, the methylation is not copied and the synthetic DNA fragments carry cytosine at those positions corresponding to 5'-methylcytosine in the genomic DNA. Thus unmethylated synthetic DNA is man-made and different to the methylated naturally occurring DNA from which it was produced by amplification

28. At the time of the earliest filing of an application that resulted in the Patents, numerous methods were available to analyze both coding and non-coding region polymorphism that do not use DNA and primer pair amplification:

a. Protein sequencing – in this method, the proteinaceous gene product is sequenced directly by determining the order of its constituent amino acids. Polymorphism at the genetic level manifests itself in the form of proteins with amino acid differences at a specific position.

b. Immunological methods – in such methods, the different binding of polymorphs of a protein to antibodies enables their identification. A particularly widely used immunological method – enzyme-linked immunosorbent assay (ELISA) – uses a heterogeneous, solid-phase enzyme immunoassay to detect the allele.

c. Northern blotting – in this method, RNA is electrophoretically separated by size, transferred ('blotted') to a membrane and interrogated by hybridisation to a labeled probe. The probe/s has/have a sequence complementary to the region of that RNA which is polymorphic and can discriminate alleles. Probes can be DNA, RNA or oligonucleotides. Because of incomplete splicing, intronic polymorphisms can be detected in this way.

29. There are also a number of methods for the detection of non-coding polymorphisms that do not require primer pair amplification at the time of the filing of the applications for the Patents, these included:

a. Restriction fragment length polymorphism (RFLP) – this method exploits the sequence specificity of a large family of DNA cleaving enzymes known as restriction endonucleases. Restriction endonucleases recognize a short sequence of DNA – usually a 6 base pair palindrome. Because the short sequence occurs many times throughout a genome, restriction endonucleases

cleave genomic DNA into a multitude of fragments. Polymorphism can destroy or create a restriction site and therefore be detected by a change in length of fragments. Thus, to detect polymorphisms using RFLP, genomic DNA samples are digested with one or more restriction endonucleases and the resultant fragments are electrophoretically separated, Southern blotted onto a membrane and interrogated by hybridisation to a probe.

b. Sequencing of cloned DNA – in this method, genomic DNA is cleaved with restriction endonucleases and 'shotgun' cloned into a vector such as a plasmid, bacteriophage or cosmid. Colony screening then enables clones containing the DNA region of interest to be identified and direct sequencing of insert DNA of clones from different individuals then enables polymorphisms to be detected.

30. As mentioned in the foregoing, in RFLP analysis it is common to use restriction endonucleases that recognize and cleave a specific six base pair palindromic sequence. Any specific six base pair sequence occurs on average every about four kilobases in genomic DNA *ceteris paribus* (there are four different bases in DNA, and if summation of GC is equal to the summation of AT, $4^6 = 4096$). RFLP analysis therefore usually relies on fragments greater than about two kilobases in length to detect polymorphisms.

31. The use of Third Wave (now Hologic) Invader Technology – which uses two oligonucleotides and signal amplification to detect alleles through non-coding polymorphisms also does not require primer pair amplification. The Invader technology is composed of two simultaneous isothermal reactions. A primary reaction detects polymorphisms associated with a specific region of the target DNA. A second reaction is used for generic readout and signal amplification. If the variation or sequence in question is present, an overlapping structure is

created with a probe and the Invader oligo on the target DNA region or sequence. The Invader Cleavase enzymes specifically cleave the primary probes that form overlapping structures with the Invader oligo, releasing the 5' flaps plus one nucleotide. In the absence of the specific target, no flap is released. The number of flaps released is relative to the amount of target in the sample, allowing for quantitative detection of the target non-coding polymorphism. Furthermore, the pending technology of nanopore single molecule DNA sequencing will not infringe the claims of the '179 Patent or the '659 Patent if used for detection of alleles through non-coding polymorphisms.

IV. THE PATENTS-IN-SUIT

32. On March 18, 1997, the '179 Patent was duly and legally issued for an "Intron Sequence Analysis Method for Detection of Adjacent and Remote Locus Alleles as Haplotypes." A true and correct copy of the '179 Patent is attached as Exhibit A.

33. On March 9, 1993, the '659 Patent was duly and legally issued for an "Intron Sequence Analysis Method for Detection of Adjacent and Remote Locus Alleles as Haplotypes." A true and correct copy of the '659 Patent is attached as Exhibit B.

34. GTG is the owner of the '179 Patent and the '659 Patent by assignment from Genetype AG, who was originally assigned the technology by the inventor Dr. Malcolm Simons, with the exclusive right to enforce and collect damages for infringement of the '179 Patent and the '659 Patent during all relevant time periods.

35. The '179 Patent and the '659 Patent claim patentable subject matter under 35 U.S.C. § 101.

36. The '179 Patent and the '659 Patent and the claims therein are presumed patent eligible, valid, and enforceable pursuant to 35 U.S.C. § 282.

37. The '179 Patent generally relates to methods of analysis of non-coding DNA sequences.

38. The Abstract of the '179 Patent relevantly provides:

> The present invention provides a method for detection of at least one allele of a genetic locus and can be used to provide direct determination of the haplotype. The method comprises amplifying genomic DNA with a primer pair that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. The primer-defined DNA sequence contains a sufficient number of intron sequence nucleotides to characterize the allele. Genomic DNA is amplified to produce an amplified DNA sequence characteristic of the allele. The amplified DNA sequence is analyzed to detect the presence of a genetic variation in the amplified DNA sequence such as a change in the length of the sequence, gain or loss of a restriction site or substitution of a nucleotide. The variation is characteristic of the allele to be detected and can be used to detect remote alleles.

39. Without limitation of the claims to be asserted in this action, and for exemplary purposes only, Independent Claim 1 of the '179 Patent reads:

> 1. A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising: a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and b) analyzing the amplified DNA sequence to detect the allele.

40. The '179 Patent was previously asserted by GTG in the matter of *Genetic Technologies Ltd. v. Applera Corp.*, Case No. C 03-1316-PJH, in the United States District for the Northern District of California ("Applera Action"). The Applera Action was ultimately settled with Applera Corporation taking a license to the '179 Patent, among others.

41. The '179 Patent was the subject of a declaratory judgment action initiated by Monsanto in the matter of *Monsanto Company v. Genetic Technologies Ltd.*, Case No. 06-cv-00989-HEA, in the United States District Court for the Eastern District of Missouri, Eastern Division ("Monsanto Action"). That Monsanto Action was ultimately settled. Monsanto has now taken three licenses to the '179 Patent, among others.

42. The '179 Patent was asserted by GTG in the matter of *Genetic Technologies Ltd. v. Beckman Coulter, Inc., et al*, Case No. 10-cv-0069-BBC, in the United States District Court for the Western District of Wisconsin ("Beckman Coulter Action"). The Beckman Coulter Action was resolved with at least Beckman Coulter, Inc., Gen-Probe, Inc., Interleukin Genetics Incorporated, Molecular Pathology Laboratory Network, Inc., Orchid Cellmark, Inc., Pioneer Hi-Bred International, Inc., and Sunrise Medical Laboratories, Inc. all taking a license to the '179 Patent, among others.

43. The '179 Patent was recently asserted by GTG in the matter of *Genetic Technologies Limited v. Agilent Technologies, Inc., et al.*, Case No. 11-cv-01389-WJM-KLM in the United States District Court for the District of Colorado ("Colorado Action"). In the Colorado Action, at least Eurofins STA Laboratories, Inc. and GeneSeek, Inc. have taken a license to the '179 Patent, among others.

44. GTG has secured over $15 million in licensing revenue for the '179 Patent since the filing of the Beckman Coulter Action in 2010.

45. In addition to the licenses identified in the preceding paragraphs, the '179 Patent and related patents have been licensed to at least the following entities: AgResearch Ltd.; ARUP Laboratories, Inc.; Australian Genome Research Facility Ltd.; GeneDX (a subsidiary of Bio Reference Laboratories); Bionomics Ltd.; BioSearch Technologies Inc.; Pfizer Animal Health; C

Y O'Connor ERADE Village Foundation (incorporating the Immunogenetics Research Foundation and the Institute of Molecular Genetics and Immunology Incorporated); Crop and Food Research Ltd.; DNA Diagnostics Ltd.; General Electric Co. and its subsidiary GE Healthcare Bio-Sciences Corp.; Genosense Diagnostics GmbH; Genzyme Corp.; Innogenetics N.V.; Kimball Genetics, Inc.; Laboratory Corporation of America Holdings, Inc.; Livestock Improvement Corporation Ltd.; MetaMorphix, Inc.; Millennium Pharmaceuticals Inc.; Myriad Genetics, Inc.; Nanogen, Inc.; New Zealand Blood Service; Optigen, L.L.C.; Ovita Ltd.; Perlegen Sciences, Inc.; Prometheus Laboratories Inc.; Qiagen, LLC.; Quest Diagnostics Inc.; Sciona, Inc.; Sequenom, Inc.; Syngenta Crop Protection AG; Thermo Fisher Scientific Inc.; TIB MOLBIOL Syntheselabor GmbH; Tm Bioscience Corporation; Gen-Probe, Inc.; and others.

46. Certain claims of the '179 Patent were subjected to an *Ex Parte* Reexamination before the United States Patent and Trademark Office ("USPTO") that was initiated by an unknown entity. On February 4, 2010, the USPTO issued a Notice of Intent to Issue Ex Parte Reexamination Certificate indicating that the subject claims were confirmed as valid without amendment. A true and correct copy of that Reexamination Certificate is attached as Exhibit C.

47. On May 10, 2012, a second *Ex Parte* Reexamination of certain Claims 1-18 and 26-32 of the '179 Patent was requested by Merial Ltd. That *Ex Parte* Reexamination request was granted on June 28, 2012. On March 29, 2013, the USPTO issued an *Ex Parte* Reexamination Certificate confirming all of the reexamed claims. A true and correct copy of the March 29, 2013 Reexamination Certificate is attached as Exhibit D. On March 1, 2013, a third *Ex Parte* Reexamination of Claims 1-18 and 26-32 of the '179 Patent was requested by Merial. On September 19, 2013, the USPTO issued an *Ex Parte* Reexamination Certificate confirming all of

the claims that were the subject of this Reexamination. A true and correct copy of the Reexamination Certificate is attached as Exhibit E.

48. The '179 Patent expired on March 9, 2010. However, GTG remains entitled to collect damages for past infringement occurring during the term of the '179 Patent pursuant to 35 U.S.C. §§ 284 and 286. Specifically, for infringement occurring in the period commencing six years from the filing date of GTG's original Complaint through March 9, 2010.

49. The '659 Patent generally relates to a method for detection of at least one allele to provide a determination of a haplotype.

50. The Abstract of the '659 Patent provides:

> The present invention provides a method for detection of at least one allele of a genetic locus and can be used to provide direct determination of the haplotype. The method comprises amplifying genomic DNA with a primer pair that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. The primer-defined DNA sequence contains a sufficient number of intron sequence nucleotides to characterize the allele. Genomic DNA is amplified to produce an amplified DNA sequence characteristic of the allele. The amplified DNA sequence is analyzed to detect the presence of a genetic variation in the amplified DNA sequence such as a change in the length of the sequence, gain or loss of a restriction site or substitution of a nucleotide. The variation is characteristic of the allele to be detected and can be used to detect remote alleles. Kits comprising one or more of the reagents used in the method are also described.

51. Without limitation as to claims to be asserted in this action and for exemplary purposes only, Independent Claim 1 of the '659 Patent reads:

> 1. A method for detection of at least one coding region allele of an HLA locus comprising amplifying genomic DNA with a primer pair that spans a non-coding region sequence selected from the group consisting of untranslated sequences between exons, 5' and 3' untranslated regions associated with a genetic locus, and spacing sequences between genetic loci, said primer pair defining a DNA sequence, said DNA sequence being in genetic linkage with said HLA locus and containing a sufficient number of said non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele.

52. The '659 Patent expired on March 9, 2010. However, GTG remains entitled to collect damages for past infringement occurring during the term of the '659 Patent pursuant to 35 U.S.C. §§284 and 286. Specifically, for infringement occurring in the period commencing six years from the filing date of this First Amended Complaint through March 9, 2010.

V. HISTOGENETICS' INFRINGEMENT

53. HistoGenetics claims to provide tissue-typing services and specialize in human leukocyte antigen ("HLA") typing services by sequenced-based typing ("SBT") for blood stem cell transplants. HistoGenetics states that it has performed millions of HLA SBT. HistoGenetics provides HLA SBT for donor registries, pharmacogenomics, donor centers, cord blood typing, transplant centers, and HLA laboratories.

54. Functional HLA genes encode protein molecules that function in antigen within the immune system. Polymorphisms in the HLA gene are a major barrier against transplanting human organs and stem cells because HLA incompatibility between the donor and recipient can lead to graft rejection or graft versus host disease.

55. By way of example only, HLA typing is one of the tissue-typing services related to the '179 Patent that HistoGenetics provided during the relevant time period. HistoGenetics performs many types of HLA typing by SBT, including HLA-A, -B, -C, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, -DPA1, and -DPB1 high resolution/allele typing. The HLA genes located within the human major histocompatibility complex on chromosome 6 are some of the most polymorphic functional genetic loci known at this time. The number of alleles for the HLA loci now total more than 8,000 with over 6,000 alleles for Class I loci (HLA-A, -B, and -C loci) and over 1,000 alleles for Class II loci (HLA-DR, -DQ, and -DP loci).

56. HistoGenetics' marketing materials state that it uses two amplification-based methods to perform its HLA typing services: (1) polymerase chain reaction ("PCR") amplification followed by nucleic acid sequencing (i.e., SBT) for high resolution typing (HistoGenetics' Gold Standard) and registry level resolution typing (HistoGenetics' Silver Standard), and (2) PCR-sequence specific oligonucleotide ("SSO") probe hybridization for low resolution typing. Accordingly, HistoGenetics uses genomic DNA and PCR amplification using a primer pair because both of these methods generate a product containing internally located polymorphisms that can be identified by either sequencing or SSO. The DNA sequence being amplified includes a non-coding region of the gene, thus it is an intrinsic part of the gene, and therefore is automatically linked to the coding region allele. The specific HLA primer pairs define the HLA gene as well as the group specific coding region alleles that will be amplified. Additionally, many primers are located in intron positions and each particular polymorphic nucleotide in the primer is linked to a specific group of coding alleles thereby yielding characteristic allele group specific amplification products. HistoGenetics' analysis of the amplified DNA sequence nucleotide to determine the presence of one of more genetic variations allows HistoGenetics to provide its HLA typing services. Thus, HistoGenetics' analysis and genotyping of the HLA gene during the term of the '179 Patent directly infringed one or more claims of at least the '179 Patent.

57. Upon information and belief, HistoGenetics has analyzed many non-coding DNA polymorphisms linked to coding region alleles using amplified DNA with a primer pair spanning a non-coding DNA region during the term of the '179 Patent in the provision of its HLA typing services. The provision of these testing services in this manner utilizes the invention as claimed in the '179 Patent and, thus, infringes upon one or more claims of at least the '179 Patent.

58. Upon information and belief, HistoGenetics had actual knowledge of the Patents during times relevant to this action through at least its awareness of GTG, the knowledge of its employees, and/or its research, development and/or patent application activities.

59. HistoGenetics advertises itself as "the global leader in HLA sequence based typing (SBT)." HistoGenetics goes on to state on its website that "[a]s a pioneer in HLA sequence based typing, we've provided millions of cost effective HLA SBT for donor registries, pharmacogenomics, donor centers, cord blood typing, transplant centers, and HLA laboratories. Because SBT is the gold standard for HLA typing, we can also find new and rare alleles missed by other methods."

60. Upon information and belief, SBT uses a method outlined in two papers authored by the founders of HistoGenetics. The first paper is Cereb, et al., Locus-specific amplification of HLA class I genes from genomic DNA: locus-specific sequences in the first and third introns of HLA-A, -B and –C alleles, *Tissue Antigens*, 45, 1. (hereinafter "Cereb 1995") is attached as Exhibit F. The second paper is Cereb, N. & Yang, S.Y., "Dimorphic primers derived from intron 1 for use in the molecular typing of HLA-B alleles," *Tissue Antigens*, 50, 74 (hereinafter "Cereb 1997") is attached as Exhibit G.

61. By way of example, Cereb 1995 describes a method using primers located in intron 1 and intron 3 of a HLA-A, -B and -C genes (Figure 2). Forward primers A, B and C are located in intron 1 and contain single nucleotide polymorphisms (SNPs). Reverse primers A, B and C are located in intron 3. These primers may be used for locus-specific amplification of the entire exon 2, intron 2, and exon 3 region of the HLA-A, -B and –C genes.

62. Forward primers A, B and C described in Cereb 1995 are degenerate primers. Degenerate primers represent two or more different nucleotide sequences and indicate

polymorphic positions in the genomic DNA which require degenerate primers to enable hybridization with any and/or all possible genomic DNA sequences. Each particular nucleotide at the polymorphic position in the non-coding region is linked to, and thereby characteristic of, a specific group of coding alleles.

63. By way of example, Cereb 1997 discloses primers derived from dimorphic sites at positions 75-77. Cereb goes on to explain that "[p]rimers using the diallelic sequences located in intron 1 include exon 2, intron 2 and exon 3 and are suitable for oligotyping, sequence-specific primer typing and direct sequencing."

64. Upon information and belief, discovery will show that HistoGenetics used methods outlined in Cereb 1995 and Cereb 1997 between March 2000 and March 2010 and that the use of these methods infringe at least one claim of the Patents.

VI. CLAIM FOR RELIEF
(Patent Infringement – U.S. Patent No. 5,612,179)

65. GTG incorporates by reference each and every allegation in paragraphs 1 through 64 as though fully set forth herein.

66. As described herein, HistoGenetics has manufactured, made, had made, used, practiced, imported, provided, supplied, distributed, sold, and/or offered for sale services that infringed one or more claims of the '179 Patent in violation of 35 U.S.C. § 271(a).

67. GTG has been damaged as a result of HistoGenetics' infringing conduct. HistoGenetics is thus liable to GTG in an amount that adequately compensates GTG for such infringement which cannot be less than a reasonable royalty, together with interest and costs as fixed by this Court under 35 U.S.C. § 284.

VII. CLAIM FOR RELIEF
(Patent Infringement – U.S. Patent No. 5,192,659)

68. GTG incorporates by reference each and every allegation in paragraphs 1 through 67 as though fully set forth herein.

69. As described herein, HistoGenetics has manufactured, made, had made, used, practiced, imported, provided, supplied, distributed, sold, and/or offered for sale services that infringed one or more claims of the '659 Patent in violation of 35 U.S.C. § 271(a).

70. GTG has been damaged as a result of HistoGenetics' infringing conduct. HistoGenetics is thus liable to GTG in an amount that adequately compensates GTG for such infringement which cannot be less than a reasonable royalty, together with interest and costs as fixed by this Court under 35 U.S.C. § 284.

VIII. JURY DEMAND

GTG hereby requests a trial by jury pursuant to Rule 38 of the Federal Rules of Civil Procedure.

IX. PRAYER FOR RELIEF

GTG requests that the Court find in its favor and against HistoGenetics, and that the Court grant GTG the following relief:

A. Judgment that one or more claims of the '179 Patent, and the '659 Patent has been directly infringed, either literally, and/or under the doctrine of equivalents, by HistoGenetics;

B. Judgment that HistoGenetics account for and pay to GTG all damages to and costs incurred by GTG because of HistoGenetics' infringing activities and other conduct complained of herein in an amount not less than a reasonable royalty;

C. That GTG be granted pre-judgment and post-judgment interest on the damages caused to it by reason of HistoGenetics' infringing activities and other conduct complained of herein; and

D. That GTG be granted such other and further relief as the court may deem just and proper under the circumstances.

Dated: December 17, 2013
Wilmington, Delaware

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