IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Control No.	To Be Assigned
In re Patent Of	Simons, *et al.*
U.S. Patent No.	5,612,179 Issued: March 18, 1997
U.S. Reexamination Cert.	5,612,179 C1 Issued: May 4, 2010
Issued From	07/949,652
Examiner	To Be Assigned
Group Art Unit	To Be Assigned
For	INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES

3239 Satellite Blvd., Duluth, Georgia 30096-4640

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REQUEST FOR *EX PARTE* REEXAMINATION

Mail Stop *Ex Parte* Reexam
Central Reexamination Unit
Attn: Box *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 35 USC §§ 301 to 307 and 37 CFR §§ 1.510 to 1.570, the undersigned hereby requests reexamination under 35 USC §§ 102 and 103 of claims 1-18 and 26-32 of United States Patent No. 5,612,179 issued to Simons *et al.* and entitled INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES ("the Patent") and US Reexamination Certificate US 5,612,179 C1 ("the Reexamination Certificate").

The Patent issued March 18, 1997 from US Application Serial No. 07/949,652 filed September 23, 1992. US Application Serial No. 07/949,652 was filed as a continuation of US Application Serial No. 07/551,239 filed July 11, 1990, which issued as US Patent No. 5,192,659 on March 9, 1993.[1] US Application Serial No. 07/551,239 was filed as a continuation-in-part of US Application Serial No. 07/465,863, filed January 16, 1990, and abandoned. US Application Serial No. 07/465,863 was filed as a continuation-in-part of US Application Serial No. 07/405,499, filed September 11, 1989, which also was abandoned. US Application Serial No. 07/405,499 was filed as a continuation-in-part of US Application Serial No. 07/398,217, filed August 25, 1989, which was also abandoned.

The Reexamination Certificate issued May 4, 2010.

Both the Patent and the Reexamination Certificate, issued to Malcolm J. Simons, and each is assigned on its face to Genetics Technologies Limited, Fitzroy, Victoria (AU).

The Patent and the Reexamination Certificate are hereinafter referred to as "the '179 patent" or "the Simons '179 patent". This Reexamination Request is being filed by a third party as to the patentee and the assignee.

The August 25, 1989 date is hereinafter referred to as the "earliest filing date on the face of the patent" and the September 23, 1992 date is hereinafter referred to as "the actual filing date of the patent." This distinction is presented because there are at least two reasons why claims 1-18 and 26-32—the claims in issue—are not entitled to the earliest filing date on the face of the patent.

Firstly, the claims in issue contain the terms "multi-allelic" and "multi-allelic genetic locus" which were not terms of art at the earliest filing date on the face of the patent or the actual filing date of the patent, and as to which there was neither written description nor enablement therefore in any of the applications in the lineage of the '179 patent.

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[1] It is the Requester's position that the patentee's designation of US Application Serial No. 07/949,652 as a continuation of US Application Serial No. 07/551,239 was incorrect because claims 1-18 and 26-32 introduced upon the filing of US Application Serial No. 07/949,652 are not entitled to the benefit of any application in the lineage of the '179 patent. Thus, US Application Serial No. 07/949,652, at least due to claims 1-18 and 26-32 introduced upon its filing, rendered US Application Serial No. 07/949,652 a continuation-in-part of US Application Serial No. 07/551,239. *See also* MPEP § 201.11 (disclosure in continuation and divisional applications must be the same as that of the prior filed application; and, since the claims that issued in the '179 patent were only first introduced on September 23, 1992, upon the filing of the application that matured into the '179 patent, the '179 patent contained new disclosure, not in the prior filed applications in the lineage of the '179 patent, and hence the application from which the '179 patent issued was a continuation-in-part of its immediate predecessor).

Secondly, Claims 1-8 fail to meet the requirements of 35 USC § 112, first paragraph, and cannot enjoy a filing date earlier than September 23, 1992 because the recitation, "analyzing the amplified DNA sequence to detect the allele" is broader than the disclosure of the applications in the lineage of the '179 patent (contrast claim 9 of the '179 patent which additionally recites, "to determine the presence of a genetic variation in said amplified sequence"). Similarly, claims 26-32 of the '179 patent recite a "A DNA analysis method" and fail to meet the requirements of 35 USC § 112, first paragraph, and cannot enjoy a filing date earlier than September 23, 1992 because that recitation, is broader than the disclosure of the applications in the lineage of the '179 patent.

Furthermore, since the original examination and previous reexamination of the '179 Patent (Control No. 90/010,318), there have been judicial decisions, including Federal Circuit and Supreme decisions, that demonstrate that claims 1-18 and 26-32 of the '179 patent fail to meet the requirements of 35 USC § 101 and thus fail to meet the requirements of Section 112, and hence only enjoy a September 23, 1992 filing date and are obvious in view of or anticipated by prior art.

In this regard, so it is crystal clear that these are appropriate issues to raise in reexamination, at the outset, mention is made of the text of MPEP § 2258, which states,

> Rejections may be made in reexamination proceedings based on intervening patents or printed publications where the patent claims under reexamination are entitled only to the filing date of the patent and are not supported by an earlier foreign or United States patent application whose filing date is claimed. For example, under 35 U.S.C. 120, the effective date of these claims would be the filing date of the application which resulted in the patent. Intervening patents or printed publications are available as prior art under In re Ruscetta, 255 F.2d 687, 118 USPQ 101 (CCPA 1958), and In re van Langenhoven, 458 F.2d 132, 173 USPQ 426 (CCPA 1972).

See also MPEP § 2163 (whether specification meets Section 112, e.g., provides adequate written description, arises when new claim presents limitation that is added or removed, and "the issue will arise in the context of determining … whether a claimed invention is entitled to the benefit

of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c)"); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) (claims to a sectional sofa comprising, *inter alia*, a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were broadened by removing the location of the control means); *Tronzo v. Biomet*, 156 F.3d at 1158-59, 47 USPQ2d at 1833 (Fed. Cir. 1998) (claims to generic cup shape were not entitled to filing date of parent application which disclosed "conical cup" in view of the disclosure of the parent application stating the advantages and importance of the conical shape); *In re Sus*, 306 F.2d 494, 504, 134 USPQ 301, 309 (CCPA 1962) ("one skilled in this art would not be taught by the written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only certain aryl radicals and certain specifically substituted aryl radicals [i.e., aryl azides] would be suitable for such purposes").

A copy of both the Patent and the Reexamination Certificate are appended hereto as Exhibit J and Exhibit K, respectively, in compliance with the requirements of 37 CFR § 1.510(b)(4).

In accordance with 37 CFR § 1.510, this Request includes the following:

(a) a payment in the amount of $2,520.00 for *ex parte* reexamination fee from Deposit Account No. 50-2354;

(b) a statement pointing out each substantial new question of patentability based on prior publications;

(c) an identification of every claim for which reexamination is requested, and a detailed explanation of the relevance and manner of applying the cited art to every claim for which reexamination is requested;

(d) a copy of each printed publication discussed in this Request (Exhibits A-K) and a listing thereof on a PTO-1449 or equivalent thereto (Exhibit L);

(e) a copy of the Simons '179 patent including the front face, for which reexamination is requested and the Reexamination Certificate issued in the patent (Exhibits J and K—respectively, the Patent as originally issued, and the Reexamination Certificate); and

(f) a certification that a copy of this Request has been served in its entirety, pursuant to 37 CFR § 1.248(a), on the patent owner at the address as provided for in 37 CFR § 1.33(c).

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-2354 that may be required.

This paper shows that there are substantial new questions of patentability ("SNQs") as to claims 1-18 and 26-32 in view of the following documents that are Exhibits hereto:

The Exhibits Hereto:

Exhibit A: DiLella AG. et al., "Tight linkage between a splicing mutation and a specific DNA haplotype in phenylketonuria", Nature. 1986 Aug 28-Sep 3;322(6082):799-803 (hereinafter "DiLella I");

Exhibit B: DiLella AG. et al., "Screening for phenylketonuria mutations by DNA amplification with the polymerase chain reaction", Lancet. 1988 Mar 5;1(8584):497-9 (hereinafter "DiLella II") ;

Exhibit C: Paul H, et al., "DNA polymorphic patterns and haplotype arrangements of the apo A-1, apo C-III, apo A-IV gene cluster in different ethnic groups", Hum Genet. 1987 Mar;75(3):264-8 (hereinafter "Paul")

Exhibit D: Funke et al. "Detection of a new Msp I restriction fragment length polymorphism in the apolipoprotein A-I gene", J Clin Chem Clin Biochem. 1987 Mar;25(3):131-4 (hereinafter "Funke");

Exhibit E: Koller et al. "Isolation of HLA locus-specific DNA probes from the 3'-untranslated region", Proc Natl Acad Sci U S A. 1984 Aug;81(16):5175-8. (hereinafter "Koller");

Exhibit F: Stetler et al. "Polymorphic restriction endonuclease sites linked to the HLA-DR alpha gene: localization and use as genetic markers of insulin-dependent diabetes." Proc Natl Acad Sci U S A. 1985 Dec;82(23):8100-4.(hereinafter "Stetler");

Exhibit G: Grumet et al. "An HLA-B locus probe clarifies endonuclease polymorphism of major histocompatibility complex class I genes." Mol Biol Med. 1983 Dec;1(5):501-9.(hereinafter "Grumet");

Exhibit H: EP414469A2, published February 27, 1991 (hereinafter "EP469")

Exhibit I.1: *Nazomi Communications, Inc., v. Samsung Telecommunications, Inc.*, No. C-10-05545 RMW (ND CA, March 21, 2012 Order Denying Motion for Summary Judgment);

Exhibit I.2: *Smartgene, Inc. v. Advanced Biological Laboratories, SA*, Civil Action No. 08-00642 (BAH) (DDC, Memorandum Opinion Granting Partial Summary Judgment, March 30, 2012) (*Smartgene*);

Exhibit I.3: Webster's Ninth New Collegiate Dictionary, pages 726, 779 (1984) (definitions of "many" and "multi") (hereinafter "Webster's");

Exhibit I.4: Wolfgang R. Mayr, "The Use of DNA polymorphisms demonstrated by means of the HLA system" Vox Sang 50: 193-197 (1986) (hereinafter "Mayr")

Exhibit I.5: Charles R. Scriver, "The PAH gene, Phenylketonuria, and a Paradigm Shift" Human Mutation 28(9), 831-845, 2007 (hereinafter "Scriver")

Exhibit J: US Patent No. 5,612,179;

Exhibit K: US Reexamination Certificate US 5,612,179 C1 ; and

A PTO-form 1449 listing the documents of Exhibits A-H and I.3 - I.5 is filed herewith as Exhibit L.

1. IDENTIFICATION OF CLAIMS FOR WHICH REEXAMINATION IS REQUESTED AND STATEMENT POINTING OUT EACH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

1.1 *Reexamination Requested of '179 Patent Claims 1-18 and 26-32*

Reexamination is requested of claims 1-18 and 26-32 (hereinafter "the claims") of the Simons '179 patent, especially in view of : DiLella I (Exhibit A), DiLella II (Exhibit B), Paul (Exhibit C), Funke (Exhibit D), Koller (Exhibit E), Stetler (Exhibit F), Grumet (Exhibit G), EP469 (Exhibit H), and Webster's (Exhibit I.3). Mayr (Exhibit I.4) is advanced to define the state of the art at the time of the earliest filing date on the face of the patent and Scriver (Exhibit I.5) is submitted to support arguments of inherency. Both Exhibits I.4 and I.5 support the SNQs presented herein.[2]

All of Exhibits A to G, I.3 and I.4 were publicly available prior to the earliest filing date on the face of the patent. Exhibits A to G evidence teaching, suggestion, and/or invention by another, of that which is claimed in Simons, prior to the earliest filing date on the face of the patent. Exhibit H was publicly available prior to the actual filing date of the patent. Exhibit I.3

[2] Exhibits I.4 and I.5 are provided as evidence showing universal facts; and, it is noted that such evidence need not antedate any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

supports that the claims in issue, claims 1-18 and 26-32, are not entitled to any date earlier than the actual filing date of the patent. Exhibit H evidences that claims 1-18 and 26-32, when properly accorded only the actual filing date of the patent, i.e., September 23, 1992, are not patentable.

1.2 ***References Relied upon for Substantial New Questions of Patentability***

Claims 1-18 and 26-32 of the '179 patent are not patentable because they are anticipated and rendered obvious in view of prior art not properly considered or never considered during the original prosecution and previous reexamination (Control No. 90/010,318). As detailed herein, these references support new anticipation and obviousness-type rejections of the claims of the '179 patent. In this regard, so it is crystal clear that this Request for Reexamination should be granted, mention is made of 35 USC § 303(a) which states: "The existence of a substantial new question of patentability is not precluded by the fact that a patent or printed publication was previously cited by or to the Office or considered by the Office." S*ee also In re Swanson*, 540 F.3d 1368 (Fed. Cir. 2008).

The pertinence of each of these references to the claimed subject matter for the '179 patent is discussed below.

DiLella I (Exhibit A), DiLella II (Exhibit B) and Funke (Exhibit D) were made of record during prosecution of the '179 patent. But DiLella I (Exhibit A) and DiLella II (Exhibit B) were not relied on in any rejection, and hence present substantial new questions of patentability, as shown herein.

The following references discussed herein were ***NOT*** made of record during the prosecution and reexamination of the '179 patent: Koller (Exhibit E), Grumet (Exhibit G), EP469 (Exhibit H) and Webster's (Exhibit I.3).

Paul (Exhibit C) and Stetler (Exhibit F) were made of record during the previous reexamination proceedings, but not applied as herein, and hence presents substantial new questions of patentability.

Webster's (Exhibit I.3) was not considered in any previous examination. It demonstrates that the terms "multi-allelic" and "multi-allelic genetic locus" could not have been supported by any application in the lineage of the '179 patent, and hence claims 1-18 and 26-32 that contain these recitations fail to meet the requirements of 35 USC § 112, first paragraph, and are only

entitled to a filing date of September 23, 1992—the date these claims were actually filed with the filing of the application that matured into the '179 patent.[3]

EP469 (Exhibit H) was not considered in any previous examination. It raises substantial new questions of patentability as it corresponds to the '179 patent, and renders obvious the '179 patent claims because those claims are not entitled to any date earlier than September 23, 1992, as discussed herein.

So it is crystal clear from the outset, the Requester asserts that claims 1-18 and 26-32 are NOT entitled to the benefit under 35 USC § 120 of any application in the lineage of the '179 patent, and hence only enjoy a filing date of September 23, 1992, the actual date that these claims were filed. Except as to its claims, Exhibit H corresponds to the '179 patent. Exhibit H was published February 27, 1991. Exhibit H is available under 35 USC § 102(b) against claims 1-18 and 26-32 of the '179 patent when they are properly accorded only their September 23, 1992 actual filing date. Because no application in the lineage of the '179 patent provides enablement or written description for claims 1-18 and 26-32 of the '179 patent, as required by Section 112, first paragraph, and because except as to claims Exhibit H corresponds to the '179 patent, the Requester asserts that Exhibit H renders claims 1-18 and 26-32 obvious. To any extent that the US Patent & Trademark Office considers any of claims 1-18 and 26-32 broader than the disclosure in any application in the lineage of the '179 patent, whereby none of those applications and Exhibit H provide Section 112, first paragraph, support for such claims, but disclose species of that which is within claims 1-18 and 26-32, the US Patent & Trademark Office may also consider that Exhibit H anticipates such claims. In this regard, mention is made of *In re Paulsen*, 30 F.3d 1475, 31 USPQ2d 1671(Fed. Cir. 1994) and *In re Baxter Travenol Labs*, 952 F.2d 388, 391, 21 USPQ2d 1281, 1285 (Fed.Cir.1992) which stand for the proposition that, "anticipation is the ultimate of obviousness."

All of the references have relevant dates before the September 23, 1992 actual filing date of the patent, and the references of Exhibits A to G, I.3 and I.4 all have relevant dates before the August 25, 1989 earliest filing date on the face of the patent. Thus, all of these references are prior art.

[3] Hence, US Application Serial No. 07/949,652, at least due to claims 1-18 and 26-32 introduced upon its filing, rendered US Application Serial No. 07/949,652 a continuation-in-part of US Application Serial No. 07/551,239.

Accordingly, as detailed herein, a substantial new question of patentability exists based on the fact that the foregoing prior art references were not cited or properly relied upon during the original prosecution of the '179 patent and teach all of the limitations of claims 1-18 and 26-32 of the '179 patent or demonstrate otherwise the unpatentability of the claims of the '179 patent.

Further still, as discussed herein, since the previous examinations of claims 1-18 and 26-32 there have been case law developments. These case law developments demonstrate that claims in issue in this Request for Reexamination, e.g., claims 26-32, fail to meet the requirements of 35 USC § 112, first paragraph, e.g., due to not meeting the requirements of 35 USC § 101. These case law developments mean that claims in issue in this Request for Reexamination are not entitled to the benefit of the earliest date on the face of the patent but rather the September 23, 1992 actual filing date on the face of the patent, and thus documents such as Exhibit H are available as prior art against the claims in issue. Accordingly, substantial new questions of patentability are also presented by the case law developments since the previous examinations.

1.3 ***Documents Made of Record During the Course of Prosecution or Previous Reexamination of the '179 Patent Require Consideration When Considered in New Light***

Exhibit A (DiLella I) was not utilized in any rejection but were made of record by the Examiner during the course of prosecution of the '179 patent.

Exhibit B (DiLella II) was not utilized in any rejection but were made of record by the Examiner during the course of prosecution of the '179 patent.

Exhibit C (Paul) was also made of record during the previous reexamination of the '179 Patent (Control No. 90/010,318).

However, with regard to Exhibits A, B and C, there are substantial new questions of patentability (SNQs) presented herein, warranting reexamination of the '179 patent.

In this Request for Reexamination the pertinent teachings of Exhibits A B and C are being brought to the attention of the US Patent & Trademark Office in a new light. In the a new manner presented herein, Exhibits A, B and C raise SNQs relating to the '179 patent claims 1-18 and 26-32.

MPEP § 2258.01 states,

> For a reexamination that was ordered on or after November 2, 2002 (the date of enactment of Public Law 107-273; see Section 13105 of the Patent and Trademark Office Authorization Act of 2002), reliance solely on old art (as the basis for a rejection) does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. For example, a SNQ may be based solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination(s), in view of a material new argument or interpretation presented in the request.

Also, MPEP § 2258 states,

> During reexamination, claims are given the broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims (In re Yamamoto, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984)). In a reexamination proceeding involving claims of an expired patent, claim construction pursuant to the principle set forth by the court in Phillips v. AWH Corp., 415 F.3d 1303, 1316, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005) (words of a claim "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art in question at the time of the invention) should be applied since the expired claim are not subject to amendment. The statutory presumption of validity, 35 U.S.C. 282, has no application in reexamination (In re Etter, 756 F.2d 852, 225 USPQ 1 (Fed. Cir. 1985)).

During reexamination proceedings, claims are construed with their broadest reasonable interpretation. *See In re Yamamoto*, 740 F.2d 1596, 1571 (Fed. Cir. 1984); MPEP § 2258. For this reason, a claim construction *Markman* order from a district court has no preclusive effect on the US Patent and Trademark Office and is not binding thereon. *See, e.g., In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1297 (Fed. Cir. 2007). Indeed, in *In re Morris*, 127 F.3d 1048,

1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997), the Federal Circuit made it clear that the US Patent & Trademark Office does not interpret claims in same manner as a court interprets claims in an infringement suit; but rather, the "PTO applies to verbiage of … claims the broadest reasonable meaning of the words …" *See also* MPEP § 2111 ("Claim Interpretation; Broadest Reasonable Interpretation"). Thus, the Requester's assertions herein of the broadest reasonable interpretation of claims in issue or terms of claims in issue are NOT the Requester's assertions of how the claims in issue or terms of claims in issue are to be construed in any US district court infringement litigation involving the Requester and the '179 patent. In any US district court infringement litigation involving the Requester and the '179 patent, the Requester is NOT bound by any assertion herein by Requester as to the broadest reasonable interpretation of claims in issue or terms of claims in issue.

Against this background, when claims 26-32 of the '179 patent are read as mandated by MPEP § 2258, Exhibit A explicitly or inherently meets or suggests all the limitations of claims 26-29 and 32 of the '179 patent, as it teaches a DNA analysis method which characterizes DNA haplotypes associated with alleles of the Phenylalanine hydroxylase (PAH) gene by identifying a mutation/polymorphism in non-coding DNA less than two kilobases in length.

When claims 26-32 of the '179 patent are read as mandated by MPEP § 2258, Exhibit B explicitly or inherently meets or suggests all the limitations of claims 26-29 and 32 of the '179 patent, as it teaches a DNA analysis method which characterizes DNA haplotypes associated with alleles of the Phenylalanine hydroxylase (PAH) gene by identifying a mutation/polymorphism in non-coding DNA less than two kilobases in length.

Also, when claims 26-32 of the '179 patent are read as mandated by MPEP § 2258, Exhibit C explicitly or inherently meets or suggests all the limitations of claims 26-29 and 32 of the '179 patent as it presents a DNA analysis method which characterizes haplotype arrangements in a gene cluster of three genes with the help of certain polymorphisms in non-coding DNA which are less than two kilobases in length.

The preamble of independent claim 26 of the '179 patent recites "A DNA analysis method". Under the broadest reasonable interpretation as mandated by MPEP § 2258, this recitation is not a limitation and may broadly refer to any method in which DNA is analyzed, examined or studied (*See also infra* at Section 3.3 concerning the claims not being entitled to any

date earlier than September 23, 1992). Therefore, Exhibit A reads on this limitation by analyzing DNA via a dideoxynucleotide chain termination method or fractionating restriction enzyme digested DNA by gel electrophoresis. Exhibit B reads on this limitation by analyzing DNA via amplification with polymerase chain reaction (PCR) and hybridization with an oligonucleotide specific probe. Exhibit C also reads on this limitation by analyzing DNA via digestion with restriction endonucleases and southern blotting followed by hybridization with labeling probes.

Furthermore, because claims 1-18 and 26-32 of the '179 patent recite "multi-allelic genetic locus" and this term and the term "multi-allelic" have no support whatsoever in any application in the lineage of the '179 patent, this recitation cannot be relied on as providing any distinction from the prior art of Exhibits A, B and C (*See also infra* at Section 3.3 concerning the claims not being entitled to any date earlier than September 23, 1992).

Accordingly, as further elaborated on herein, Exhibits A, B and C, either individually or in combinations as discussed below, anticipate or render obvious claims 1-18 and 26-32. Moreover, as elaborated on herein, art cited against the '179 patent was not properly considered or applied during original prosecution, and was not properly considered or applied in the previous reexamination (Control No. 90/010,318). Specifically, Exhibit A, Exhibit B or Exhibit C inherently or explicitly anticipate or render obvious claims 1-18 and 26-29 and 32 of the '179 patent. Thus, there are SNQs presented by this paper and it is respectfully asserted that this Request for Reexamination should be granted.

1.4 ***Documents Made of Record During the Course of Prosecution or Previous Reexamination of the '179 Patent Presented in New Light and in Further View of New Art Require Consideration***

Exhibit D (Funke) were not relied upon in any rejection during the prosecution the '179 patent but was referred to as being maintained in a 35 USC § 103 rejection during the prosecution of the parent of the '179 patent, U.S. patent 5,192,659. It was made of record by the Examiner during the previous reexamination of the '179 patent when it was put forth to support a rejection of obviousness.

Exhibit F (Stetler) was not relied upon in any rejection but was made of record by the Examiner during the previous reexamination of the '179 patent (Control No. 90/010,318).

The following Exhibits are new: Koller (Exhibit E), and Grumet (Exhibit G).

Exhibits D, E, F and G are relied upon herein, in combination with other Exhibits hereto, to demonstrate the obviousness of claims for which reexamination is requested.

Thus, there are SNQs with respect to the references presented herewith, warranting reexamination of the '179 patent. More in particular, in this Request for Reexamination, the pertinent teachings of Exhibits D-G are being brought to the attention of the US Patent & Trademark Office in a new light, and in a new manner, whereby Exhibits D-G raise substantial new questions of patentability (SNQs) relating to the '179 patent claims 1-18 and 26-32.

Thus, it appears that art was not properly considered or properly applied in the prosecution or original reexamination of the '179 patent. Specifically, Exhibit A, Exhibit B or Exhibit C, alone, or when combined with other references (Exhibits of Exhibits D-G), render obvious claims 1-18 and 26-32.

1.5 ***New References Relied upon for a Substantial New Question of Patentability***

Koller (Exhibit E), Grumet (Exhibit G), EP469 (Exhibit H) ,Webster's (Exhibit I.3), Mayr (Exhibit I.4), and Scriver (Exhibit I.5) are new references to be considered.

Claims 26-32 for which reexamination is requested of the Simons '179 patent are obvious under § 103 in view of DiLella I (Exhibit A) or DiLella II (Exhibit B), further in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G).

Claims 26-32 for which reexamination is requested of the Simons '179 patent are obvious under § 103 in view of Paul (Exhibit C) as evidenced by Funke (Exhibit D), further in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G).

Claims 1-18 for which reexamination is requested of the Simons '179 patent are obvious under § 103 in view of DiLella II (Exhibit B), further in view of Koller (Exhibit E) and Stetler (Exhibit F).

There is motivation to combine herein cited references since herein cited references relate to polymorphisms associated with genes that have more than one allele, wherein the polymorphisms are located in regions of non-coding DNA.

Exhibit I.3 is are dictionary pages from a 1984 dictionary. Exhibit I.3 was not previously considered in any examination and that claims 1-18 and 26-32 of the '179 patent cannot enjoy any date earlier than September 23, 1992 due to the terms "multi-allelic" and "multi-allelic genetic locus" (*See* Section 3.3, *infra*).

The claims of the '179 patent are rendered obvious by EP469 as the '179 patent claims do not enjoy a filing date prior to September 23, 1992. To any extent that the US Patent & Trademark Office considers any of claims 1-18 and 26-32 broader than the disclosure in any application in the lineage of the '179 patent, whereby none of those applications and Exhibit H provide Section 112, first paragraph, support for such claims, but disclose species of that which is within claims 1-18 and 26-32, the US Patent & Trademark Office may also consider that Exhibit H anticipates such claims. In this regard, mention is made of *In re Paulsen*, 30 F.3d 1475, 31 USPQ2d 1671(Fed. Cir. 1994) and *In re Baxter Travenol Labs*, 952 F.2d 388, 391, 21 USPQ2d 1281, 1285 (Fed.Cir.1992) which stand for the proposition that, "anticipation is the ultimate of obviousness."

Mayr (Exhibit I.4) is advanced to define the state of the art at the time of the earliest filing date on the face of the patent and Scriver (Exhibit I.5) is submitted to support arguments of inherency. Both Exhibits I.4 and I.5 support the SNQs presented herein.[4]

2. SUMMARY OF SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY

From Exhibits A through H, Substantial New Questions (SNQs) of Patentability as herein further discussed include:

2.1 *Claims Deemed Anticipated*

2.1.1 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella I (Exhibit A)

2.1.2 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella II (Exhibit B)

2.1.3 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)

2.2 *Claims Deemed At Least Obvious*

2.2.1 Claims 26-32 are obvious in view of DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G).

2.2.2 Claims 26-32 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G).

[4] Exhibits I.3, I.4 and I.5 are provided as evidence showing universal facts; and, it is noted that such evidence need not antedate any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

2.2.3 Claims 26-32 are obvious in view of Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G).

2.2.4 Claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and Stetler (Exhibit F) (or claims 1-18 are obvious in view of Exhibit B in view of Exhibits E, F, I.4 and I.5[5])

2.2.5 Claims 1-18 and 26-32 are obvious in view of or, to any extent broader than the disclosure of the applications in the lineage of the '179 patent, anticipated by EP469 (Exhibit H) (or claims 1-18 and 26-32 are obvious or to any extent broader than the disclosure of the applications in the lineage of the '179 patent, anticipated by Exhibit H and Exhibit I.3[6])

3. A BRIEF SUMMARY OF THE DOCUMENTS CITED BY REQUESTER

Requester, in the following text, provides a brief discussion of the documents cited in support of this Request for Reexamination, with it mentioned that Exhibits E, G, H, I.3, I.4 and I.5 were ***NOT*** before the Examiner during original prosecution and the previous reexamination (Reexamination Control No. 90/010,318). The text in Section 5 provides a detailed discussion of the SNQs and proposed rejections of the claims. Also, as discussed in the main text and in footnotes, Exhibits I.3, I.4 and I.5 are submitted as evidence of universal facts, and are included in alternative (typically parenthetical) statements of SNQs and rejections of the claims, to any extent such documents that demonstrate universal facts need also be included in statements of SNQs and rejections, to ensure that this Request for Reexamination is complete and precipitates granting of this Request and a Reexamination Certificate cancelling all of claims 1-18 and 26-32.

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[5] While Exhibits I.4 and I.5 are provided to demonstrate evidence of universal facts, *cf.* MPEP 2131.01, to any extent they needs to be included in a rejection or statement of SNQ, they are so included in the parenthetical. More than one reference can be employed in an anticipation rejection when the second reference is cited for evidence of a universal fact; and, references for demonstrating universal facts need not be before any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

[6] While Exhibits I.3 is provided to demonstrate evidence of universal facts, *cf.* MPEP 2131.01, to any extent it needs to be included in a rejection or statement of SNQ, it is so included in the parenthetical. More than one reference can be employed in an anticipation rejection when the second reference is cited for evidence of a universal fact; and, references for demonstrating universal facts need not be before any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

3.1 *Koller (Exhibit E) Presents SNQs*

Koller or Exhibit E presents a new teaching not previously considered in the prosecution history or the previous reexamination. Specifically, it has not been previously considered that Exhibit E teaches a DNA analysis method in which DNA in the HLA class I gene locus is analyzed. The HLA system refers to Human Leukocyte Antigen and is the name of the Major Histocompatibility Complex (MHC) in humans. The analysis involves digesting the genomic DNA with restriction endonucleases and probing the resulting fragments which are characteristic of a particular gene haplotype with a locus specific probe. Exhibit E teaches a locus specific probe that stretches over 490 bp and contains all of the HLA-A2 3' untranslated region and 72 bp of 3' flanking DNA. Hence, the non-coding DNA associated with said specific haplotype is not more than two kilobases in length.

Thus, Exhibit E raises substantial new questions of patentability as to the '179 patent claims because Exhibit E renders obvious claims 1-18 and 26-32 of the '179 patent and specifically dependent claim 30 when considered in view of Exhibits A-C. Also, Exhibit E raises SNQs as to claims 1-18 in view of the universal facts demonstrated by Exhibits I.4 and I.5; *see* discussion in Section 5, *infra*.

Exhibit E was not properly considered and applied during the prosecution and previous reexamination of the '179 patent claims (Control No. 90/010,318). That is, in the present request for reexamination, the pertinent teachings of Exhibit E are being brought to the attention of the USPTO in a new light. It is presented herein in a new manner that Exhibit E raises substantial new questions of patentability (SNQs) relating to the '179 patent claims 26-32.

Exhibit E, individually or in combination, thus raises substantial new questions of patentability as to the claims of the '179 patent.

3.2 *Grumet (Exhibit G) Presents SNQs*

Grumet or Exhibit G presents a new teaching not previously considered in the prosecution history or the previous reexamination. Specifically, it has not been previously considered that Exhibit G teaches a DNA analysis method in which DNA in the HLA class I gene locus is analyzed. That the analysis involves probing to analyze southern blots of genomic DNA. Exhibit G teaches the intragenic localization of an HLA-allele specific restriction

endonuclease site. The locus specific probe that stretches over 180 nucleotides comprising the last (7th) intron of the original B7 gene. Hence, the non-coding DNA associated with said specific haplotype is not more than two kilobases in length.

Thus Exhibit G raises substantial new questions of patentability as to the '179 patent claims because Exhibit G renders obvious claims 26-32 of the '179 patent and specifically dependent claim 30 when considered in view of Exhibits A-C.

Exhibit G was not properly considered and applied during the prosecution and previous reexamination of the '179 patent claims (Control No. 90/010,318). That is, in the present request for reexamination the pertinent teachings of Exhibit G are being brought to the attention of the USPTO in a new light. It is presented herein in a new manner that Exhibit G raises substantial new questions of patentability (SNQs) relating to the '179 patent claims 26-32.

Exhibit G, individually or in combination, thus raises substantial new questions of patentability as to the claims of the '179 patent.

3.3 ***EP469 (Exhibit H) and Webster's (Exhibit I.3) Present SNQs***

MPEP § 2217 states,

> The statement applying the prior art may, where appropriate, point out that claims in the patent for which reexamination is requested are entitled only to the filing date of the patent and are not supported by an earlier foreign or United States patent application whose filing date is claimed. For example, the effective date of some of the claims in a patent which resulted from a continuing application under 35 U.S.C. 120 could be the filing date of the continuing application since those claims were not supported in the parent application. Therefore, intervening patents or printed publications are available as prior art. See In re Ruscetta, 255 F.2d 687, 118 USPQ 101 (CCPA 1958), In re van Langenhoven, 458 F.2d 132, 173 USPQ 426 (CCPA 1972). See also MPEP § 201.11.

MPEP § 2258 states,

> Rejections may be made in reexamination proceedings based on intervening patents or printed publications where the patent claims under reexamination are entitled only to the filing date of the patent and are not

> supported by an earlier foreign or United States patent application whose filing date is claimed. For example, under 35 U.S.C. 120, the effective date of these claims would be the filing date of the application which resulted in the patent. Intervening patents or printed publications are available as prior art under In re Ruscetta, 255 F.2d 687, 118 USPQ 101 (CCPA 1958), and In re van Langenhoven, 458 F.2d 132, 173 USPQ 426 (CCPA 1972).

See also MPEP § 2163 (whether specification meets Section 112, e.g., provides adequate written description, arises when new claim presents limitation that is added or removed, and "the issue will arise in the context of determining … whether a claimed invention is entitled to the benefit of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c)"); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998); *Tronzo v. Biomet*, 156 F.3d at 1158-59, 47 USPQ2d at 1833 (Fed. Cir. 1998); *In re Sus*, 306 F.2d 494, 504, 134 USPQ 301, 309 (CCPA 1962).

Particularly instructive cases include *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) and *Tronzo v. Biomet*, 156 F.3d at 1158-59, 47 USPQ2d at 1833 (Fed. Cir. 1998). In *Gentry Gallery*, claims to a sectional sofa comprising, *inter alia*, a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were **broadened** by removing the location of the control means. In *Tronzo*, claims to generic cup shape were not entitled to filing date of parent application which disclosed "conical cup" in view of the disclosure of the parent application stating the advantages and importance of the conical shape. Consistent with *Gentry Gallery* and *Tronzo*, claims 1-18 and 26-32 do not enjoy the filing date of any application in the lineage of the '179 patent and only can be accorded the date they were filed, namely September 23, 1992.

Claims 1-8 fail to meet the requirements of 35 USC § 112, first paragraph, and cannot enjoy a filing date earlier than September 23, 1992 because the recitation, "analyzing the amplified DNA sequence to detect the allele" is broader than the disclosure of the applications in the lineage of the '179 patent (contrast claim 9 of the '179 patent which additionally recites, "to determine the presence of a genetic variation in said amplified sequence").

Similarly, claims 26-32 of the '179 patent recite a "A DNA analysis method" and fail to meet the requirements of 35 USC § 112, first paragraph, and cannot enjoy a filing date earlier than September 23, 1992 because that recitation, is broader than the disclosure of the applications in the lineage of the '179 patent.

For example, following the broadest reasonable interpretation mandate of MPEP § 2258, "A DNA analysis method" broadly reads on any method in which DNA is analyzed, examined or studied. In the '179 patent specification, DNA analysis is a step that follows DNA amplification (*see* '179 patent, col. 3, line 65 to col. 4, line 5 ("Genomic DNA is amplified to produce an amplified DNA sequence characteristic of the allele. The amplified sequence is analyzed to detect the presence…") and col 16, lines 9-14 ("Analysis of the Amplified DNA sequence. As discussed previously, the method used to analyze the amplified DNA sequence to characterize the allele(s)….")). It is noted that the "Reasons for Allowance" in the prosecution history of the '179 patent states that the closet prior art "does not teach the amplification of coding and non-coding regions". It is respectfully brought to the attention of the US Patent & Trademark Office that the limitation of requiring primers or amplifying coding and non-coding regions of DNA are not recitations of claims 26-32, and thus the recitation of "A DNA analysis method" is therefore, under the broadest reasonable interpretation mandated by MPEP § 2258, not as narrow as asserted in the Reasons for Allowance. Simply, the term "A DNA analysis method" must be construed under the broadest reasonable interpretation mandated by MPEP § 2258 to mean any method in which DNA is analyzed, examined or studied, and accordingly broadens the claims beyond the disclosure in the applications in the lineage of the '179 patent, whereby claims 26-32 can only enjoy a September 23, 1992 filing date.

Also with respect to claims 26-32, applying the broadest reasonable interpretation mandated by MPEP § 2258, the term "polymorphisms characteristic of the allele" may broadly either refer to features generally associated with an allele or features that uniquely define the allele, whereas in the specification, the term is not defined but is used in reference to a polymorphism in non-coding DNA that is in linkage disequilibrium with the allelic polymorphism, and hence not defined or used in the manner it may be used in the claims. It is noted that the "Reasons for Allowance" in the prosecution history of the '179 patent states in reference to the prior art, "they do not teach nor reasonably suggest that primers be used to

amplify a non-coding region that is in linkage to an allele sequence". However, this makes no sense because there is no such recitations in claims 26-32 and under the broadest reasonable interpretation mandated by MPEP § 2258, the term "polymorphisms characteristic of the allele" cannot have be construed in claims 26-32 as set forth in the Reasons for Allowance. The term "polymorphisms characteristic of the allele", because under the broadest reasonable interpretation mandated by MPEP § 2258 can have several meanings, and is not defined in the '179 patent specification, but is used in reference to a polymorphism in non-coding DNA that is in linkage disequilibrium with the allelic polymorphism of requiring linkage between DNA sequences, the term "polymorphisms characteristic of the allele" causes claims 26-32 to fail to meet the requirements of 35 USC § 112, first and second paragraphs, whereby for this reason too, these claims only enjoy a September 23, 1992 filing date.

With respect to all of claims 1-18 and 26-32, the terms "multi-allelic" and "multi-allelic genetic locus" were introduced into the claims of the '179 patent via a preliminary amendment filed on September 23, 1992. Due to these terms, claims 1-18 and 26-32 also enjoy no filing date earlier than September 23, 1992. The specification of the applications in the lineage of the '179 patent makes the following exemplary unclear references with regard to the number of alleles being considered:

- The Abstract: "The present invention provides a method for detection of at least one allele of a genetic locus…"
- Page 15, line 3: "For example, the least polymorphic HLA locus is DPA which currently has four recognized alleles"
- Page 15, line 17: "When about eight or more alleles are to be distinguished, as for the DQA1 locus and more variable loci…."

At either the earliest filing date on the face of the patent or the September 23, 1992 actual filing date of the the patent (due to the issued claims having first been filed in the September 23, 1992 Preliminary Amendment), the term "multi-allelic" had no ordinary meaning in the art, and it is never used in any application in the lineage of the '179 patent.

Rather, the applications in the lineage of the '179 patent call for at least one allele, four alleles, about eight or more alleles, fourteen alleles, twenty-four alleles and thirty-four alleles. In contrast, the patentee has apparently relied on "multi-allelic genetic loci" and defined it as "at

least three alleles" (*See* Request for Reexamination, Control No. 90/010,318 at p. 4-5; Appendix A at p. 15).

However, for the universe of at least one allele, four alleles, about eight or more alleles, fourteen alleles, twenty-four alleles and thirty-four alleles, up to an infinite number of alleles—the metes and bounds of "multi-allelic"—are unclear and neither described nor enabled, especially as the common meaning can be more than one allele, and somehow the patentee selects at least three with no upper limit.

Exhibit I.3 bolsters the conclusion that claims 1-18 and 26-32 are entitled to no filing date earlier than September 23, 1992 due to the terms "multi-allelic" and "multi-allelic genetic locus." Webster's (Exhibit I.3) shows that when applying the broadest reasonable interpretation standard mandated by MPEP § 2258, "multi" can mean "more than one" and according to that dictionary, "multi" also can mean "many" and hence "an infinite large number of ... things" (*see also* Exhibit I.3 at definition of "many" at page 726). As an initial matter, Exhibit I.3 demonstrates that the definition adopted by the patentee for "multi-allelic genetic loci", i.e., "at least three alleles" (*see* Request for Reexamination, Control No. 90/010,318 at p. 4-5; Appendix A at p. 15), is wholly inconsistent with the plain meaning of "multi". Moreover, Exhibit I.3 shows that under the broadest reasonable interpretation as mandated by MPEP § 2258, "multi" can have a number of different meanings, up to infinity. Accordingly, the undefined terms "multi-allelic" and "multi-allelic genetic locus" could not have distinguished the claims from the prior art, and could only have rendered the claims as failing to meet the requirements of 35 USC § 112, first and second paragraphs, whereby the claims are only entitled to the date they were introduced, namely September 23, 1992.

In addition to the lack of description and enablement for the term "multi-allelic", there is also a lack of description and enablement flowing from the lack of clarity for the term "multi-allelic" because giving the term its broadest reasonable interpretation pursuant to MPEP § 2258, there may also be two possible common interpretations of the term "multi-allelic genetic locus". The term "multi-allelic genetic locus" is either a particular genetic locus is occupied by one gene having more than one allele (as seen in Exhibit A or in Exhibit B) or the genetic locus could be occupied by more than one gene having one or more alleles (as seen in Exhibit C). Accordingly, for this reason too, the term "multi-allelic genetic locus" causes claims 1-18 and 26-32 to fail to

meet the requirements of both 35 USC § 112 first and second paragraphs, and thereby only enjoy a September 23, 1992 filing date.

Further, the first paragraph of Section 112 of Title 35 (35 USC) states,

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Section 101 of Title 35 states,

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

If a claim fails to meet the requirements of 35 USC § 101, then it necessarily fails to meet the requirements of 35 USC § 112, first paragraph. For example, MPEP § 2164.07 directs that a claim to nonuseful or inoperative subject matter under Section 101 necessarily fails to meet the how-to-use aspect of the enablement requirement of Section 112; *see also In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429 434 (CCPA 1971) (if "compositions are in fact useless, appellant's specification cannot have taught how to use them"). Likewise, Section 112, first paragraph speaks of "the invention" and if a claim is to subject matter that is not an invention under Section 101, the claim necessarily fails to meet the requirements of Section 112, first paragraph.

Against this background, since the original examination and previous reexamination of the '179 Patent (Control No. 90/010,318), there have been judicial decisions, including Federal Circuit and Supreme decisions, that demonstrate that claims 1-18 and 26-32 of the '179 patent fail to meet the requirements of Section 112, only enjoy a September 23, 1992 filing date and are obvious in view of or anticipated by prior art, including Exhibit H.

In *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office* (*Myriad*), 653 F.3d 1329, 99 U.S.P.Q.2d (BNA) 1398 (Fed. Cir. 2011), *cert. granted, judgment vacated, and*

remanded sub nom. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., No. 11-725, 2012 WL 986819 (U.S. Mar. 26, 2012) (remanding to the Federal Circuit for further consideration in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012)), the Federal Circuit held that claims involving merely comparing DNA molecules were not an invention under 35 USC § 101.

Thereafter, in *Mayo Collaborative Services v. Prometheus Laboratories Inc.*, 132 S. Ct. 1289, 101 USPQ2d 1961 (2012) (*Prometheus*), the US Supreme Court ruled that the asserted claims in Prometheus's patents on a diagnostic method were not eligible for patent protection, i.e., were not an invention under 35 USC § 101 because they covered laws of nature and ''the steps in the claimed processes (apart from the natural laws themselves) involve well understood, routine, conventional activity previously engaged in by researchers in the field.''

In *Nazomi Communications, Inc., v. Samsung Telecommunications, Inc.*, No. C-10-05545 RMW (ND CA, March 21, 2012 Order Denying Motion for Summary Judgment; Exhibit I.1), the Court, calling Supreme Court's *Prometheus* decision "*Mayo*", states,

> In *Mayo*, the Court recognized that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." Slip op. at 2. In distinguishing between processes that are patent eligible and those that are impermissibly broad, the Court focused on whether the process contains additional steps that "transform[] the process" from one that pre-empts all use of a natural law "into an inventive application of the formula." *See id.* at 3, 11-12; *see also id.* at 14-15 (discussing favorably English case in which "the claimed process included not only a law of nature but also several unconventional steps . . . that confined the claims to a particular, useful application of the principle"). The Court rejected the claims at issue because the claims did little more than recite a law of nature and add the instruction "apply the law." *See id.* at 8-11. The Court found that the same reasoning applied in [*Gottschalk v. Benson*, 409 U.S. 63 (1972)], as the claim there "did not differ significantly from a claim that just said 'apply the algorithm.'" *Id.* at 16.

In *Smartgene, Inc. v. Advanced Biological Laboratories, SA*, Civil Action No. 08-00642 (BAH) (DDC, Memorandum Opinion Granting Partial Summary Judgment, March 30, 2012; Exhibit I.2), the Court found that the claims at issue failed to be an invention under Section 101 and discussed the Supreme Court's *Prometheus* decision as follows:

> Specifically, the *Prometheus* Court distilled the guideposts from its earlier section 101 cases into the following "warnings." The Supreme Court warned "against interpreting patent statutes in ways that make patent eligibility 'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws],'" *id.* (quoting *Flook*, 437 U.S. at 593), and warned against "upholding patents that claim processes that too broadly preempt the use of a natural law." *Id.* (citing *O'Reilly v. Morse*, 56 U.S. 62, 112-120). A "process that focuses upon the use of a natural law" must "contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* (quoting *Flook*, 437 U.S. at 594). The Court found that the patent at issue failed this test, explaining that "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* The Court further observed that "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries," and thereby allowing monopolies of unforeseeable scope. *Id.*

Furthermore, the March 21, 2012 Memorandum of Andrew H. Hirschfeld, Associate Commissioner for Patent Examination Policy, to the United States Patent and Trademark Office Examining Corps, that provides guidance on the USPTO's application of *Prometheus* (available at http://www.uspto.gov/patents/law/exam/mayo_prelim_guidance.pdf), states (with bold emphasis in the original and underlining emphasis added),

> … Examiners must continue to ensure that claims, particularly process claims, are not directed to an exception to eligibility such that the claim amounts to a monopoly on the law of nature, natural phenomenon, or abstract idea **itself**. In addition, to be patent-eligible, a claim that includes an exception should include other elements or combination of elements such that, in practice, the claimed product or process amounts to significantly **more than** a law of nature, a natural phenomenon, or an abstract idea with conventional steps specified at a high level of generality appended thereto.
>
> If a claim is effectively directed to the exception itself (a law of nature, a natural phenomenon, or an abstract idea) and therefore does not meet the eligibility requirements, the examiner should reject the claim under section 101 …

Claims 1-8 of the '179 patent call 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." Claims 9-18 call for a similar "detection" with the only difference being that the "analyzing" is "to determine the presence of a genetic variation in said amplified sequence"—but, this difference is without anything more, i.e., without any recitation of what steps (or claim elements) one performs to make such a determination. Claims 1-18 are akin to the claims in Prometheus, highlighted in by Mr. Hirschfeld's March 21, 2012 Memorandum to the Examining Corps on how to apply *Prometheus* in examination. Claim 1-18 do little more than recite a law of nature and add the instruction "apply the law." Claims 1-18 provide "a law of nature, a natural phenomenon, or an abstract idea with conventional steps specified at a high level of generality appended thereto" that is required to be rejected under Section 101 by Mr. Hirschfeld's March 21, 2012 Memorandum to the Examining Corps on how to apply *Prometheus* in examination.

Claims 26-32 of the '179 patent call for a DNA analysis method for determining coding region alleles of a multi-allelic genetic locus. The ONLY recited step of the claimed methods is "identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length." Here, claims 26-32 of the '179 patent are akin to those rejected by the *Prometheus* Court. Claims 26-32 of the '179 patent do little more than recite a law of nature and add the instruction "apply the law." Claims 26-32 provide "a law of nature, a natural phenomenon, or an abstract idea with conventional steps specified at a high level of generality appended thereto" that is to be rejected under Section 101 according to Mr. Hirschfeld's March 21, 2012 Memorandum to the Examining Corps on how to apply *Prometheus* in examination.

Claims 1-18 and 26-32 of the '179 patent are not patent-eligible subject matter under 35 USC § 101 because in the words of the *Smartgene* Court, there are no "other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself," and in the words of Mr. Hirschfeld's March 21, 2012 Memorandum to the Examining Corps on how to apply *Prometheus* in examination, claims 1-18 and 26-32 fail to provide "significantly **more than** a law of nature, a natural phenomenon, or an abstract idea with conventional steps specified at a high level of generality appended thereto."

Accordingly, claims 1-18 and 26-32 of the '179 patent also enjoy only a September 23, 1992 filing date due to *Myriad*, *Prometheus*, and their progeny, e.g., *Smartgene*, and Mr. Hirschfeld's March 21, 2012 Memorandum to the Examining Corps on how to apply *Prometheus* in examination, showing that claims 1-18 and 26-32 of the '179 patent are not an invention under 35 USC § 101, and thus do not meet the requirements of 35 USC § 112, first paragraph.

Based on the foregoing, claims 1-18 and 26-32 are not entitled to a filing date earlier than September 23, 1992.[7] Since claims 1-18 and 26-32 are not entitled to a filing date earlier than

[7] *See also* MPEP §§ 201.11; 706.03(a); 2107.01.

MPEP § 201.11 instructs that under 35 USC § 120 a claim is entitled to the benefit of the filing date of an earlier filed US application if the earlier filed application meets 35 USC § 112, first paragraph as to the subject matter of the claim (citing, for example, *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 47 USPQ2d 1829 (Fed. Cir. 1998); *In re Scheiber*, 587 F.2d 59, 199 USPQ 782 (CCPA 1978).

September 23, 1992 these claims are obvious in view of or anticipated by prior art, including Exhibit H (or Exhibit H and I.3).

More in particular, Exhibit H, which corresponds to the '179 patent, renders obvious claims 1-18 and 26-32 as it is available against the '179 patent pursuant to 35 USC § 102(b) because claims 26-32 only enjoy a September 23, 1992 filing date.

To any extent that the US Patent & Trademark Office considers any of claims 1-18 and 26-32 broader than the disclosure of the applications in the lineage of the '179 patent, whereby none of those applications and Exhibit H provide Section 112, first paragraph, support for such claims, but disclose species of that which is within claims 1-18 and 26-32, the US Patent & Trademark Office may also consider that Exhibit H anticipates such claims. In this regard, mention is made of *In re Paulsen*, 30 F.3d 1475, 31 USPQ2d 1671(Fed. Cir. 1994) and *In re Baxter Travenol Labs*, 952 F.2d 388, 391, 21 USPQ2d 1281, 1285 (Fed.Cir.1992) which stand for the proposition that, "anticipation is the ultimate of obviousness." For example, based on the above discussion, it is respectfully asserted that the recitation of claims 1-8 of "analyzing the amplified DNA sequence to detect the allele", the recitation of claims 26-32 of a "DNA analysis method", and the recitations of "multi-allelic" and "multi-allelic genetic locus" of claims 1-18

MPEP § 201.11 also instructs that if the claim of later filed US application is only entitled to the filing date of later filed application, the claim can "read on" published, publicly used or sold, or patented subject matter (e.g., as in a genus-species relationship) and a rejection under 35 USC § 102 is proper (citing, for example, *Mendenhall v. Cedarapids Inc.*, 5 F.3d 1557, 28 USPQ2d 1081 (Fed. Cir. 1993); *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971); *In re Hafner*, 410 F.2d 1403, 161 USPQ 783 (CCPA 1969); *In re Ruscetta*, 255 F.2d 687, 118 USPQ 101 (CCPA 1958); *In re Steenbock*, 83 F.2d 912, 30 USPQ 45 (CCPA 1936); *Ex parte Hageman*, 179 USPQ 747 (Bd. App. 1971)).

MPEP § 706.03(a) instructs issuing rejections under Section 101 for claims to laws of nature, natural phenomenon, and abstract ideas.

MPEP § 2107.01 instructs that a deficiency under 35 USC § 101 also creates a deficiency under 35 USC § 112, first paragraph, stating directly that, "Courts have also cast the 35 U.S.C. 101/ 35 U.S.C. 112 relationship such that 35 U.S.C. 112 presupposes compliance with 35 U.S.C. 101, citing, *inter alia*, *In re Ziegler*, 992 F.2d 1197, 1200-1201, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993), for the statement, "If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law … under 35 U.S.C. § 112."

Accordingly, the herein demonstration that claims 1-18 and 26-32 fail to meet the requirements of 35 USC § 101 warrant a holding that claims 1-18 and 26-32 fail to meet the requirements of 35 USC § 112, first paragraph, and are not entitled to the benefit of earlier applications under 35 USC § 120. The demonstration herein that claims 1-18 and 26-32 fail to meet the requirements of 35 USC § 112, first paragraph due to the recitations of these claims also means that these claims are not entitled to the benefit of earlier applications under 35 USC § 120. Exhibit H is thus available as prior art against claims 1-18 and 26-32 and Exhibit H, either alone or in combination with Exhibit I.3 anticipates or renders obvious claims 1-18 and 26-32, for the reasons given herein throughout this paper. This has not been considered in any previous examination of the '179 patent and presents an SNQ. Reexamination on this basis, and a Reexamination Certificate cancelling claims 1-18 and 26-32 of the '179 patent are respectfully requested.

and 26-32 broadened these claims beyond the disclosure in the applications in the lineage of the '179 patent such that Exhibit H, disclosing species within claims 1-18 and 26-32 anticipated those claims, as well as rendered them obvious.

Accordingly, EP469 which corresponds to the '179 patent but was published on February 27, 1991—more than one year before September 23, 1992—is available as art under 35 USC § 102(b), and by itself or with I.3 renders obvious or anticipates claims 1-18 and 26-32 of the '179 patent, and raises substantial new questions of patentability.

4. THE '179 PATENT CLAIMS IN ISSUE

Claims 1-18 and 26-32 of the '179 patent and the reissue certificate of the '179 patent read as follows:

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.

2. The method of claim 1 wherein said amplified DNA sequence includes at least about 300 nucleotides corresponding to non-coding region sequences.

3. The method of claim 1 wherein said non-coding region sequence is adjacent to an exon encoding said allele.

4. The method of claim 1 wherein said amplified DNA sequence is characteristic of at least one nonadjacent allele.

5. The method of claim 1 wherein said amplified DNA sequence is characteristic of at least one adjacent allele and at least one nonadjacent allele.

6. The method of claim 5 wherein said amplified DNA sequence includes at least about 1,000 nucleotides corresponding to non-coding region sequences.

7. The method of claim 1 wherein said genetic locus has at least four alleles.

8. The method of claim 1 wherein said genetic locus has at least eight alleles.

9. A method for detection of at least one 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 allele and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and

b) analyzing said amplified DNA sequence to determine the presence of a genetic variation in said amplified sequence to detect the allele.

10. The method of claim 9 wherein said variation in said amplified DNA sequence is a variation in the length of the primer-defined amplified DNA sequence.

11. The method of claim 9 wherein said variation in said amplified DNA sequence is a change in the presence of at least one restriction site in the primer-defined amplified DNA sequence.

12. The method of claim 9 wherein said variation in said amplified DNA sequence is a change in the location of at least one restriction site in the primer-defined amplified DNA sequence.

13. The method of claim 9 wherein said variation in said amplified DNA sequence is a substitution of at least one nucleotide in the primer-defined amplified DNA sequence.

14. The method of claim 9 wherein said genetic locus is a major histocompatibility locus.

15. The method of claim 9 wherein said allele is associated with a monogenic disease.

16. The method of claim 15 wherein said monogenic disease is cystic fibrosis.

17. The method of claim 9 wherein at least about 70% of said primer-defined amplified DNA sequence corresponds to non-coding region sequences.

18. The method of claim 9 wherein said primer-defined amplified DNA sequence is from 300 to 500 nucleotides in length.

26. A DNA analysis method for determining coding region alleles of a multi-allelic genetic locus comprising identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length.

27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.

28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.

29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.

30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.

31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.

32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.

5. DETAILED EXPLANATION UNDER 37 CFR 1.510(B) POINTING OUT EACH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

The herein-cited references generally show DNA analysis methods used to determine coding regions of a genetic locus having more than one allele by identifying sequence polymorphisms present in the non-coding region that are a feature of the coding region with the non-coding region being not more than two kilobases in length. More in particular, these references demonstrate that at the time the '179 patent was filed, the concept of analyzing DNA to identify coding regions based on polymorphisms in the non-coding regions, which were also understood to be conserved and important, was known.

5.1 *Discussion of Claims Deemed Anticipated*

Claims 26-29 and 32 of the Simons '179 patent are expressly or inherently anticipated under § 102(b) by Exhibit A (DiLella I) , Exhibit B (DiLella II) and Exhibit C (Paul).

The following analysis uses the broadest reasonable meaning of the claims, which the Patent Office is required to apply. MPEP § 2258 (quoted above); *see also In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002).

Claim 26 of the '179 patent, after the original reexamination, with claim elements broken up for ease of comparison reads:

[a] A DNA analysis method

[b] for determining coding region alleles of a multi-allelic genetic locus

[c] comprising identifying sequence polymorphisms characteristic of the alleles,

[d] wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence,

[e] said non-coding region sequence being not more than about two kilobases in length.

In Exhibit A, DNA was subjected to digestion by restriction endonucleases and gel electrophoresis to identify a single base mutation in intron 12 which is a feature of a mutant gene allele. More in particular, with reference to the above-quoted text of claim 26 of the '179 patent, Exhibit A explicitly discloses elements [a], [b], [c], [d] and [e].

Exhibit A specifically discloses [a] methods of analyzing DNA which include digestion with restriction endonucleases and gel electrophoresis and DNA sequencing by the dideoxynucleotide chain termination method [b] multiple haplotypes of the PAH gene locus that are present in a population [c] identifying mutations that are a feature of a specific allele or haplotype [d] characterizing the mutations as a silent nucleotide substitution (A→G) in the third base of codon 232 (Gln) and a G to A transition at the 5' splice donor site of intron 12 and [e] analysis method which involve a 114-base pair fragment containing 24 bp of a downstream intron or 2 kb restriction fragments containing non-coding DNA sequences that are hybridized to specific oligonucleotide probes.

In Exhibit B, DNA was subjected to PCR amplification and hybridization with a specific oligonucleotide probe to identify a single base mutation in intron 12 which is a feature of a mutant gene allele. More in particular, with reference to the above-quoted text of claim 26 of the '179 patent, Exhibit B explicitly discloses elements [a], [b], [c], [d] and [e].

Exhibit B specifically discloses [a] methods of analyzing DNA which include primer amplification of a sub-genomic DNA with PCR [b] multiple haplotypes of the PAH gene locus that are present in a population [c] identifying mutations that are a feature of a specific allele [d] characterizing the mutation as a single base substitution at the exon 12/intron 12 boundary and [e] analysis method involving the amplification of a 245 base pair (bp) region containing exon 12

and the flanking intronic sequences. Attention is directed to the fact the disclosure relates to the amplification of both coding and non-coding DNA as Exhibit B expressly states that primers were selected with primer A being complementary to the antisense DNA strand of intron 11, 58-77 nucleotides upstream of exon 12 and Primer B is complementary to the sense DNA strand of exon 12 , 33-52 nucleotides downstream of exon 12.

Therefore, as a matter of fact, Exhibit B performed every step of the claimed method in the claims of the '179 patent. Thus, the claims are inherently anticipated by Exhibit B.

In Exhibit C, DNA is isolated, digested with restriction endonucleases, southern blotted and hybridized with specific labeling probes. Identified restriction sites are polymorphic in the gene locus and are associated with different haplotypes that may indicate linkage disequilibrium between different alleles. More in particular, with reference to the above-quoted text of claim 26 of the '179 patent, Exhibit C explicitly discloses elements [a], [b], [c], [d] and [e].

Exhibit C specifically discloses [a] methods of analyzing DNA which include digestion with restriction endonucleases, southern blotting, hybridization and labeling with specific probes[b] multiple haplotypes of the gene locus containing the genes A-1, C-III and A-IV [c] identifying polymorphic restriction sites indicative of a specific haplotype, [d] mapping the polymorphic site to the 5' flanking region of the A1 gene [e] digestion with Taq-1 results in fragments 1.3 kb and 1.7 kb or 1.9 kb which are less than two kilobases in length.

Thus, Exhibit A or Exhibit B or Exhibit C alone or when either Exhibit A or Exhibit B or Exhibit C is combined with other references cited herein discloses DNA analysis methods which encompass all the limitations of the claims as issued.

Exhibit A, Exhibit B or Exhibit C alone or in combination with Exhibits E-G (as further shown below) explicitly and inherently discloses the method of the claims of the '179 patent. Exhibit D further supports the disclosure of Exhibit C.

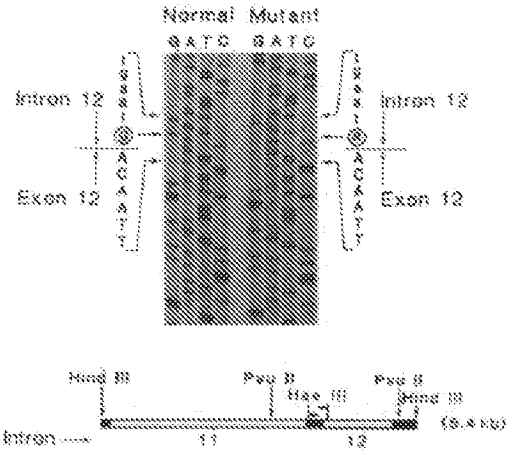
The following analysis uses the broadest reasonable meaning of the claims, which the Patent Office is required to apply. MPEP § 2258 (quoted above); *see also In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002).

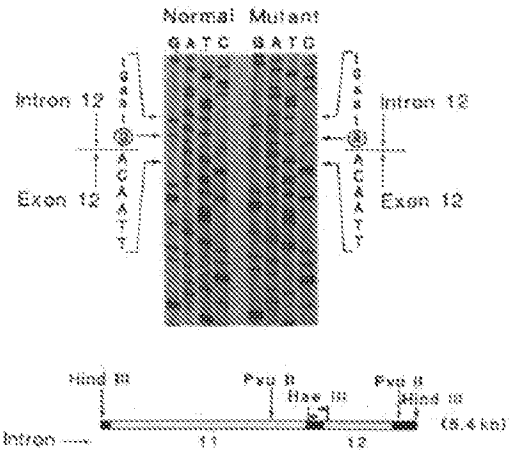
As disclosed in the following claim charts (and to any extent necessary any other text herein pertaining to the Exhibits employed in the anticipation SNQs and suggested rejections), the prior art references teach all of the claim limitations of the '179 patent.

5.1.1 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella I (Exhibit A)

In view of all text herein concerning Exhibit A, including the following table, claims 26-29 and 32 are anticipated by DiLella I (Exhibit A); and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

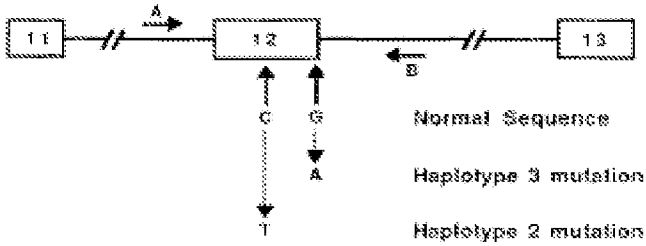
Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella I (Exhibit A)	
The Simons '179 patent	DiLella I (Exhibit A)
Claim 26. A DNA analysis method…..	**Exhibit A** teaches a "Direct hybridization analysis using specific oligonucleotide probes" (Abstract) and sequencing by the dideoxynucleotide chain-termination method (p. 800)
…..for determining coding region alleles of a multi-allelic genetic locus comprising….	**Exhibit A** teaches using "a full-length human PAH complementary DNA clone to identify and map eight restriction fragment-length polymorphisms (RFLPs) at the human PAH locus. These RFLPs segregate in a mendelian manner and concordantly with the mutant alleles in PKU kindreds." (See p. 799) and using "RFLPs to identify 12 haplotypes of normal and PKU alleles in the Danish population, and observed a strong association among distinct RFLP haplotypes and PKU alleles." (p. 799-800)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence,…	**Exhibit A** teaches "that the mutation is tightly associated with a specific restriction fragment-length polymorphism haplotype among mutant alleles" (Abstract) and "The first phenylketonuria mutation identified in the human phenylalanine hydroxylase gene is a single base substitution (GT→ AT) in the canonical 5'-splice donor site of intron 12." (Abstract)

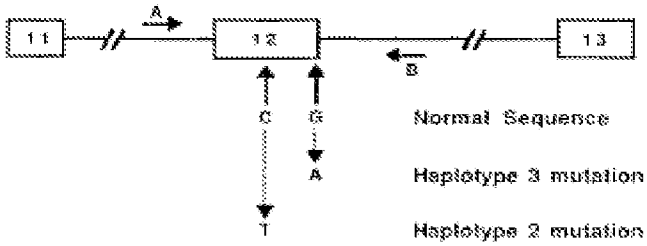
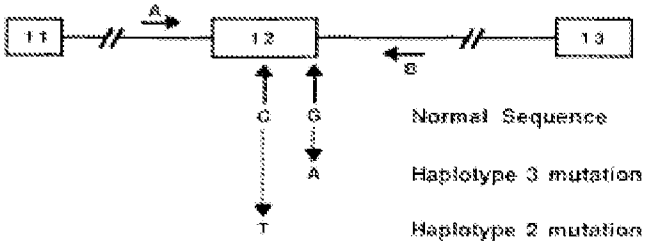
…..said non-coding region sequence being not more than about two kilobases in length.	**Exhibit A** teaches " Sequence analysis of the 5'-donor splice site of exon 12. The 114-base pair (bp) *Hae*III fragment (bottom) containing 90 bp of exon 12 and 24 bp of the downstream intron was inserted into the *Sma* I site of M13mp18 and sequenced in both directions (arrows) by the dideoxynucleotide chain-termination method." (figure legend of Fig. 1 on p. 800)  "*Pvu*II digestion of the 12-kilobase (kb) *Eco*RI fragment isolated from both the normal (N) and mutant (M) gene clones generated a 2-kb fragment containing the entire exon 12 plus flanking intronic sequences. Under the hybridization conditions used, the normal probe hybridized only to the 2-kb *Pvu*II fragment of the normal gene (Fig. 2a, middle panel), and the mutant probe hybridized specifically to the mutant gene (Fig. 2a, right panel)." (See p. 801)
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit A** teaches that the mutation in the 5' donor splice site of intron 12 which abuts exon 12. Hence, there are no bases in between the polymorphism in intron 12 and exon 12 and that falls within the limitation of "within five kilobases".
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit A** teaches that the mutation in the 5' donor splice site of intron 12 which abuts exon 12. Hence, there are no bases in between the polymorphism in intron 12 and exon 12 and that falls within the limitation of "within two kilobases".
Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable	**Exhibit A** teaches that the mutation in the 5' donor splice site of intron 12 which abuts exon 12. Intron 12 is an intervening sequence which is adjacent to exon 12.

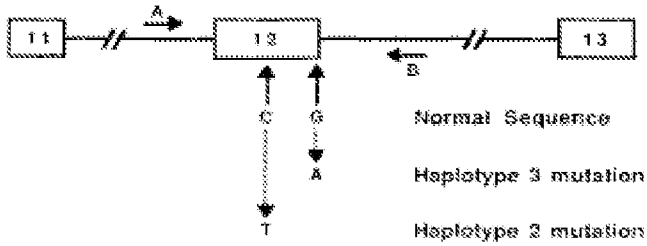
Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella I (Exhibit A)	
The Simons '179 patent	DiLella I (Exhibit A)
exon of the locus.	
Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.	
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit A** teaches "Sequence analysis of the 5'-donor splice site of exon 12. The 114-base pair (bp) *Hae*III fragment (bottom) containing 90 bp of exon 12 and 24 bp of the downstream intron was inserted into the *Sma* I site of M13mp18 and sequenced in both directions (arrows) by the dideoxynucleotide chain-termination method." (figure legend of Fig. 1 on p. 800) 

5.1.2 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella II (Exhibit B)

In view of all text herein concerning Exhibit B, including the following table, claims 26-29 and 32 are anticipated by DiLella II (Exhibit B); and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella II (Exhibit B)	
The Simons '179 patent	DiLella II (Exhibit B)
Claim 26. A DNA analysis method…..	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)
…..for determining coding region alleles of a multi-allelic genetic locus comprising….	**Exhibit B** teaches "Twelve restriction fragment length polymorphism (RFLP) haplotypes at the PAH locus in the northern European population have been characterised, and about 90% of the PKU alleles in this population are confined to RFLP haplotypes 1-4. Different combinations of the mutant RFLP haplotypes contribute to the allelic and clinical diversity of PKU." (p. 497)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence,….	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry;" (Summary) "The mutation associated with haplotype 3 is caused by a single base substitution at the exon 12/ intron 12 boundary…" (p. 497)
…..said non-coding region sequence being not more than about two kilobases in length.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig1)." 

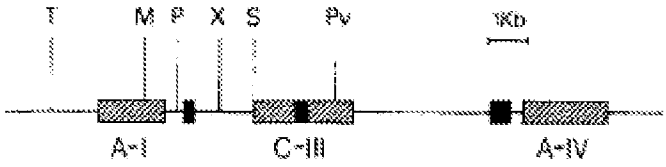
Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella II (Exhibit B)	
The Simons '179 patent	DiLella II (Exhibit B)
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig 1)." 
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig 1)." 
Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.	**Exhibit B** teaches that the single base substitution is at the exon/12/intron 12 boundary (specifically at the 5' donor splice site of intron 12 as mentioned in Exhibit A) . Intron 12 is an intervening sequence which is adjacent to exon 12.

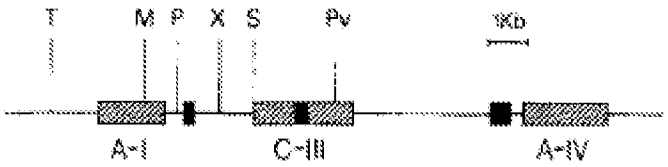
Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by DiLella II (Exhibit B)	
The Simons '179 patent	DiLella II (Exhibit B)
Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.	
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig1)." 

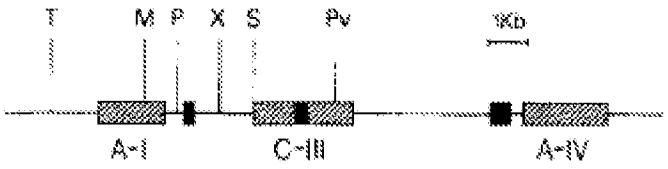
5.1.3 Claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)

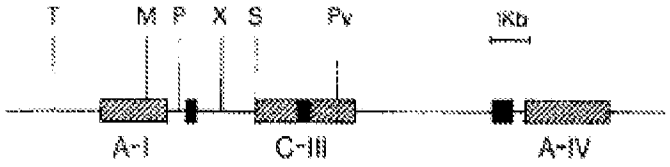
As shown by the herein text concerning Exhibit C, including the following table, claims 26-29 and 32 are anticipated by Paul (Exhibit C); and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

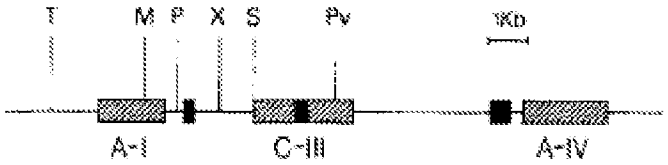
Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
The Simons '179 patent	Paul (Exhibit C)
Claim 26. A DNA analysis method for determining coding region alleles of a multi-allelic genetic locus comprising	**Exhibit C** teaches a genetic locus having three genes, A-1, C-III and A-IV. "Linkage disequilibrium was evident between some of the alleles and a total of seven haplotypes were identified

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
	among the different races" (Abstract) "The polymorphic sites are with Taq-1 at the 5' end of the A-1 gene, with Msp-1 in the third intron of the A-1 gene, with Pst-1 in the intergenic sequence between the A-1 and C-III genes, with Sst-1 in the 3' non-coding region of the C-III gene, and with Pvu-II in the third intron of the C-III gene." (p. 264, abstract)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length.	**Exhibit C** teaches "The polymorphic sites are with Taq-1 at the 5' end of the A-1 gene, with Msp-1 in the third intron of the A-1 gene, with Pst-1 in the intergenic sequence between the A-1 and C-III genes, with Sst-1 in the 3' non-coding region of the C-III gene, and with Pvu-II in the third intron of the C-III gene." (p. 264, abstract)  Fig. 1. Map of the A-1, C-III, A-IV gene region showing the polymorphic restriction sites. T = Taq-1, P = Pst-1, X = Xmn-1, S = Sst-1, P = Pst-1, Pv = Pvu-II, M = Msp-1. ▩, Genes; ■, repetitive elements
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit C** teaches: "The A-1 probe was a genomic probe consisting of a HindIII/Pst-1 fragment and the C-III probe was a full length cDNA" (p. 265, left column, 4th paragraph) "Digestion with Taq-1 and hybridization with an A-1 probe shows one invariant band of 1.3 kb and a two allele polymorphism with bands at 1.7 kb (T2 allele) or 1.9 kb (T1 allele). The polymorphic site maps to the 5' flanking region of the A-1 gene." (p. 265, left column, last paragraph) "Digestion with Msp-1 and hybridization with an A-1 probe detects a two allele polymorphism with bands at 1.7 kb (M2 allele) or 1.0kb and 0.7kb (M1 allele). The polymorphism is in the third intron of the A-1 gene" (p.

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
	265, right column, 1st paragraph) "Digestion with Pst-1 and hybridization with an A-1 probe shows a two allele allele polymorphism with bands at 2.2 kb (P1 allele) or 3.2 kb (P2 allele). The polymorphic site maps to the intergenic sequence between the A-1 and C-III genes." (p. 265, right column, 2nd paragraph). "Sst-1 digestion and hybridization with an A-1 probe gives an invariant band of 5.6 kb and a two allele polymorphism with bands at 4.2 kb (S1 allele) or 3.2 kb (S2 allele). The polymorphism site is located in the 3' non-coding region of the C-III gene" (p. 265, right column, 4th paragraph) "Digestion with Pvu II and hybridization with a C-III probe shows an invariant band of 1.6 kb and a two allele polymorphism with bands at 0.8 kb (Pv2 allele0 and 1 kb (Pv1 allele). The polymorphic site is located in the third intron of the C-III gene" (p. 266, right column, 1st paragraph)  **Fig. 1.** Map of the A-1, C-III, A-IV gene region showing the polymorphic restriction sites. T = Taq-1, P = Pst-1, X = Xmn-1, S = Sst-1, P = Pst-1, Pv = Pvu-II, M = Msp-1. ▩, Genes; ■, repetitive elements
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit C** teaches: "The A-1 probe was a genomic probe consisting of a HindIII/Pst-1 fragment and the C-III probe was a full length cDNA" (p. 265, left column, 4th paragraph) "Digestion with Taq-1 and hybridization with an A-1 probe shows one invariant band of 1.3 kb and a two allele polymorphism with bands at 1.7 kb (T2 allele) or 1.9 kb (T1 allele). The polymorphic site maps to the 5' flanking region of the A-1 gene." (p. 265, left column, last

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
	paragraph) "Digestion with Msp-1 and hybridization with an A-1 probe detects a two allele polymorphism with bands at 1.7 kb (M2 allele) or 1.0kb and 0.7kb (M1 allele). The polymorphism is in the third intron of the A-1 gene" (p. 265, right column, 1st paragraph) "Digestion with Pst-1 and hybridization with an A-1 probe shows a two allele allele polymorphism with bands at 2.2 kb (P1 allele) or 3.2 kb (P2 allele). The polymorphic site maps to the intergenic sequence between the A-1 and C-III genes." (p. 265, right column, 2nd paragraph). "Digestion with Pvu II and hybridization with a C-III probe shows an invariant band of 1.6 kb and a two allele polymorphism with bands at 0.8 kb (Pv2 allele0 and 1 kb (Pv1 allele). The polymorphic site is located in the third intron of the C-III gene" (p. 266, right column, 1st paragraph)  **Fig. 1.** Map of the A-1, C-III, A-IV gene region showing the polymorphic restriction sites. T = Taq-I, P = Pst-1, X = Xmn-1, S = Sst-1, P = Pst-1, Pv = Pvu-II, M = Msp-1. ▩, Genes; ■, repetitive elements
Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.	**Exhibit C** teaches**:** "Digestion with Pst-1 and hybridization with an A-1 probe shows a two allele allele polymorphism with bands at 2.2 kb (P1 allele) or 3.2 kb (P2 allele). The polymorphic site maps to the intergenic sequence between the A-1 and C-III genes." (p. 265, right column, 2nd paragraph). "Sst-1 digestion and hybridization with an A-1 probe gives an invariant band of 5.6 kb and a two allele polymorphism with bands at 4.2 kb (S1 allele) or 3.2 kb (S2 allele). The polymorphism site is located in the 3' non-coding region of

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
	the C-III gene" (p. 265, right column, 4th paragraph)  **Fig. 1.** Map of the A-1, C-III, A-IV gene region showing the polymorphic restriction sites. T = Taq-I, P = Pst-I, X = Xmn-I, S = Sst-I, P = Pst-1, Pv = Pvu-II, M = Msp-1. ▨, Genes; ■, repetitive elements
Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.	
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit C** teaches**:** "The A-1 probe was a genomic probe consisting of a HindIII/Pst-1 fragment and the C-III probe was a full length cDNA" (p. 265, left column, 4th paragraph) "Digestion with Msp-1 and hybridization with an A-1 probe detects a two allele polymorphism with bands at 1.7 kb (M2 allele) or 1.0kb and 0.7kb (M1 allele). The polymorphism is in the third intron of the A-1 gene" (p. 265, right column, 1st paragraph) "Digestion with Pvu II and hybridization with a C-III probe shows an invariant band of 1.6 kb and a two allele polymorphism with bands at 0.8 kb (Pv2 allele0 and 1 kb (Pv1 allele). The polymorphic site is located in the third intron of the C-III gene" (p. 266, right column, 1st paragraph)

Anticipation under 35 USC § 102: claims 26-29 and 32 of the Simons '179 patent are anticipated under § 102(b) by Paul (Exhibit C)	
	 Fig. 1. Map of the A-I, C-III, A-IV gene region showing the polymorphic restriction sites. T = Taq-I, P = Pst-1, X = Xmn-1, S = Sst-1, P = Pst-1, Pv = Pvu-II, M = Msp-1. ▩, Genes; ■, repetitive elements

5.2 *Claims Deemed At Least Obvious*

As disclosed in the following claim charts, the prior art references teach all of the claim limitations of the '179 patent. Furthermore, where a combination of references is relied upon, it is clear that all of the references deal directly with DNA analysis methods which identify polymorphisms in non-coding DNA that are related to coding region alleles of a genetic locus.

With particular regard to claims 1-18 being rendered obvious, claim 1 of the '179 patent, with claim elements broken up for ease of comparison reads:

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

Claim 1 is rendered obvious as Exhibit B discloses [a] the identification of multiple haplotypes of the PAH gene locus that are present in a population [b] primer amplification of a sub-genomic DNA with PCR inclusive of intronic non-coding sequences [c] identifying mutations that are a feature of a specific allele such as a single base substitution at the exon

12/intron 12 boundary [d] analysis method involving the amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences and [e] confirming haplotypes with oligonucleotides specific for the allelic mutations. Attention is directed to the fact the disclosure of Exhibit B relates to the amplification of both coding and non-coding DNA as Exhibit B expressly states that primers were selected with primer A being complementary to the antisense DNA strand of intron 11, 58-77 nucleotides upstream of exon 12 and Primer B is complementary to the sense DNA strand of exon 12, 33-52 nucleotides downstream of exon 12.

Furthermore, at the time of the earliest filing date on the face of the patent, it was known to one of ordinary skill in the art that genomic DNA may be used to reveal polymorphisms in both coding and non-coding DNA and that non-coding DNA encompassed 97% of the genome. Exhibit I.4 which was published in 1984 is submitted to indicate the state of the art at a time prior to the earliest filing date on the face of the patent. Exhibit F sets out that polymorphisms located within intronic sequences are linked to the gene HLA-DRα which has multiple alleles and Exhibit E discloses the identification of HLA locus specific probes from the 3'-untranslated region which indicates that sequences present in a non-coding region may be specific for or linked to coding region sequences. Based on the disclosures of Exhibits B, E and F, it would be obvious to one of skill in the art studying genes with multiple alleles at the time of the earliest filing date on the face of the patent to conduct PCR to indentify polymorphisms in non-coding sequences linked to coding sequences.

Claims 2 and 6 refer to amplified DNA sequences including at least about 300 nucleotides and at least about 1000 nucleotides that correspond to non-coding regions, respectively.

MPEP § 2144.05 states,

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid

concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

The '179 patent does not put forward any criticality in the number of non-coding nucleotides being at least about 300 or at least about 1000, and hence claims 2 and 6 are rendered obvious by the disclosure of Exhibit B in which a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences is amplified and the disclosure of Exhibit E in which allele specific probes from 3'-untranslated regions have lengths of 490 bp and 358 bp.

Claims 3, 4, 5, 7 and 8 are also rendered obvious in view of the disclosures of Exhibit B, E and F relating to gene loci with multiple alleles which inherently include adjacent and non-adjacent (or remote) alleles. Exhibit B discloses mutations in the PAH gene which is responsible for Phenylketonuria (PKU), and more than 500 different PAH alleles have been recorded in the PAH database as stated in Exhibit I.5. Exhibit I.5 is advanced to demonstrate that the PAH gene discussed in Exhibit B inherently has multiple alleles. Hence, clearly claims 7 and 8, reciting at least 4 or at least 8 alleles respectively, are rendered obvious. With such a vast number of alleles that include both adjacent or non-adjacent (or remote) alleles, it would be evident to one of ordinary skill in the art that polymorphisms in non-coding sequences could be linked to both adjacent and non-adjacent (or remote) alleles. Therefore, claims 3, 4 and 5 are rendered obvious.

Furthermore, claim 9 of the '179 patent, with claim elements broken up for ease of comparison reads:

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

Exhibit B renders claim 9 obvious as it specifically discloses [a] the identification of multiple haplotypes of the PAH gene locus that are present in a population [b] primer amplification of a sub-genomic DNA with PCR inclusive of intronic non-coding sequences [c] identifying mutations that are a feature of a specific allele such as a single base substitution at the exon 12/intron 12 boundary [d] analysis method involving the amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences and [e] confirming haplotypes with oligonucleotides specific for the allelic mutations or genetic variations.

Claims 10, 11, 12 and 13 refer to the variations being a variation in the length of primer-defined amplified DNA sequence, a change in the presence of at least one restriction site in the primer-defined amplified DNA sequence, a change in the location of at least one restriction site in the primer-defined amplified DNA sequence and a substitution of at least one nucleotide in the primer-defined amplified DNA sequence, respectively.

Exhibit B clearly teaches a single base substitution in the exon 12/intron 12 boundary that is characteristic of a mutant PAH allele and Exhibit F further discloses polymorphisms in restriction sites which yield different fragment lengths when digested by the same pair of restriction endonucleases. It would have been evident to one of skill in the art at the time of the earliest filing date on the face of the patent that different restriction fragment lengths may result from changes in the presence or in the location of at least one restriction site. Given the

combination of the disclosures of Exhibits B and F, claims 10, 11, 12 and 13 are clearly rendered obvious.

In addition, claim 14 is rendered obvious as Exhibit E discloses locus specific sequences in non-coding genomic DNA of HLA-A and B genes and as mentioned previously, HLA refers to the Human Leukocyte Antigen system and is the name of the MHC in humans. Exhibit B further discloses mutant alleles of PKU which is a characteristic monogenic disease and is one of the most commonly inherited genetic disorders. Hence, claim 15 is rendered obvious and one of ordinary skill in the art would be motivated to detect alleles of other monogenic diseases like Cystic Fibrosis by arriving at linkages between polymorphisms in non-coding regions and coding alleles. Exhibit E discloses that the pHLA-1 allele specific probe is a 358 base pair fragment that only contains 3'-untranslated sequences and this indicates that 100% of the probe corresponds to non-coding regions sequences. This renders both claims 17 and 18 obvious.

In summary, all of claims 1-18 are rendered obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F) (or all of claims 1-18 are rendered obvious by Exhibit B in view of Exhibits E, F, I.4 and I.5[8]).

5.2.1 Claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)

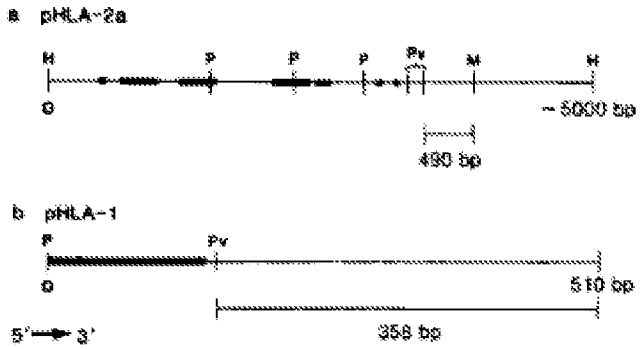
Exhibit A describes a DNA analysis method that involves identifying a polymorphism or mutation in the PAH gene present in intron 12 and its association with a particular genetic haplotype. Exhibit E and F relate to HLA class I locus specific probes that provide information on polymorphisms in HLA class I genes and Exhibit G relates to HLA class II locus specific probes that provide information on polymorphisms in HLA class II genes. The motivation to combine these references can be found since all documents are related to the characterization of polymorphisms associated with genes having one or more allele. *See also* Section 5.1.1, *supra*, for support regarding Exhibit A. In view of all text before the following tables, all text herein concerning the Exhibits in the following tables, and the following tables, claims 26-32 are

[8] While Exhibits I.4 and I.5 are provided to demonstrate evidence of universal facts, *cf.* MPEP 2131.01, to any extent they needs to be included in a rejection or statement of SNQ, they are so included in the parenthetical. More than one reference can be employed in an anticipation rejection when the second reference is cited for evidence of a universal fact; and, references for demonstrating universal facts need not be before any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

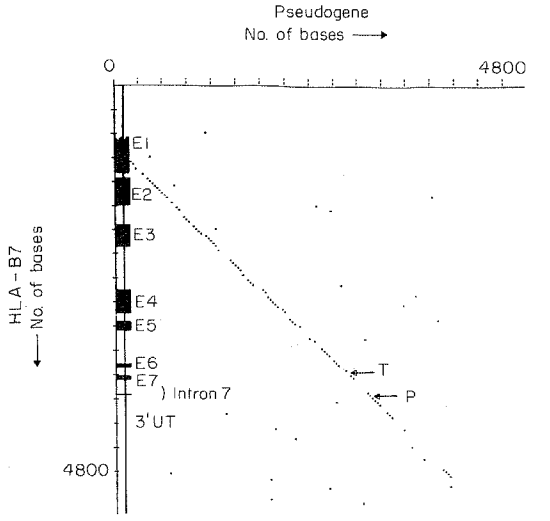
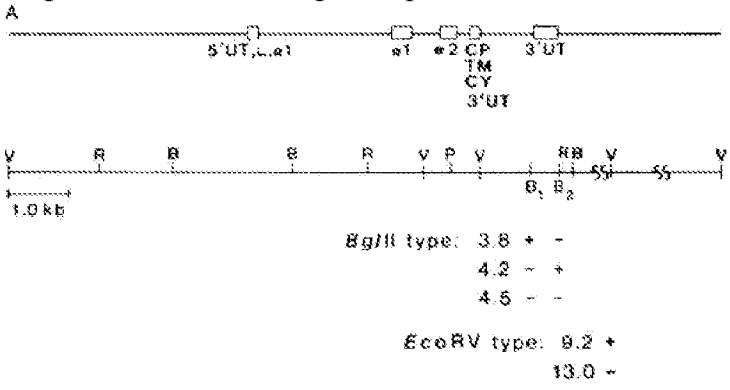
obvious in view of Exhibit A in view of Exhibits E, F and G; and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
Claim 26. A DNA analysis method for determining coding region alleles of a multi-allelic genetic locus comprising	**Exhibit E** teaches Today, > 20 HLA-A and >40 HLA-B alleles have been described (p. 5175, left column, 1st paragraph) **Exhibit G** teaches "Use of the probe to analyze Southern blots of genomic DNA from unrelated individuals provides the first direct demonstration of intragenic localization of an HLA allele-specific restriction endonuclease site." (p. 501, abstract) **Exhibit F** teaches "To identify RFLPs associated with the HLA-DRa gene, genomic DNA from a variety of individuals was digested with nine different endonucleases, electrophoresed, and analyzed by blot hybridization with the pDRa-1 probe."(p. 8101, Results)

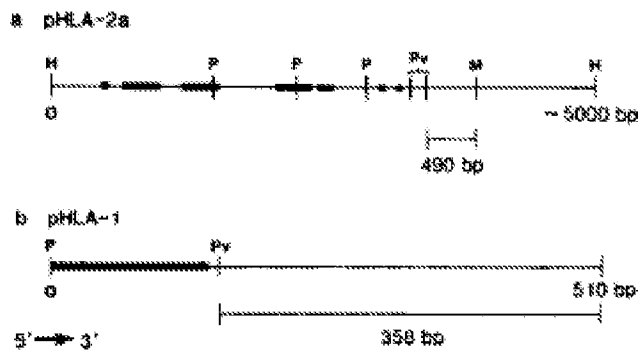
Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)

The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) "The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems". (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)

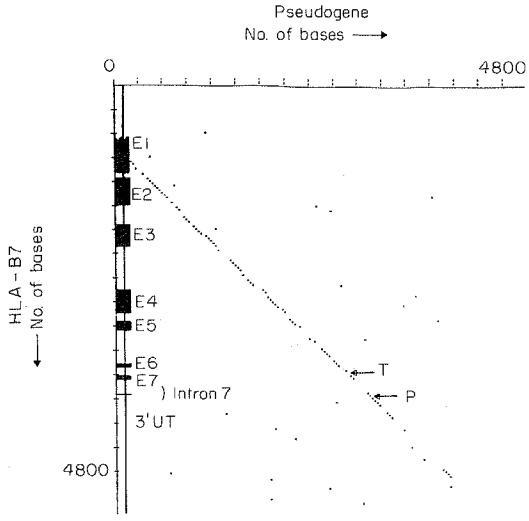
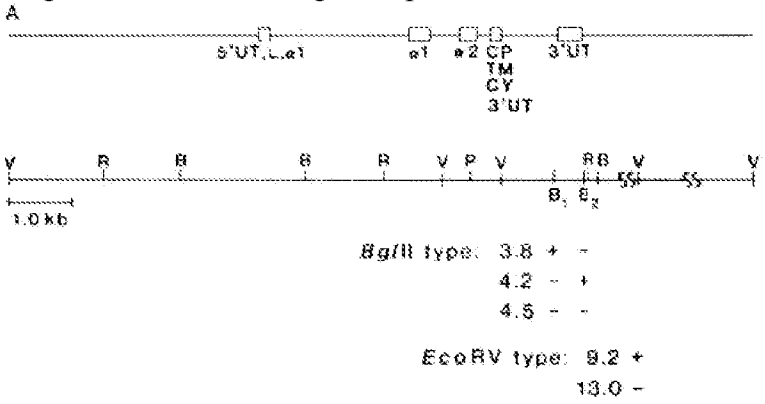
Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)

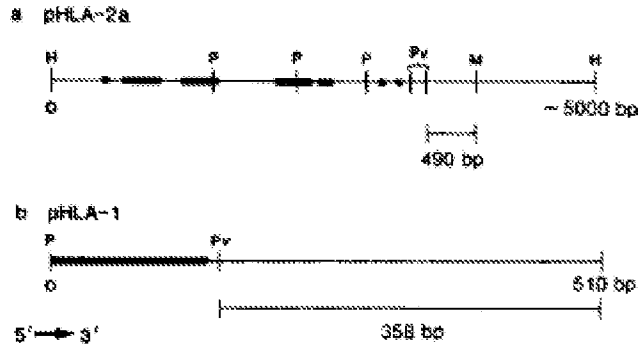
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	 (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(p. 8101, Results) 

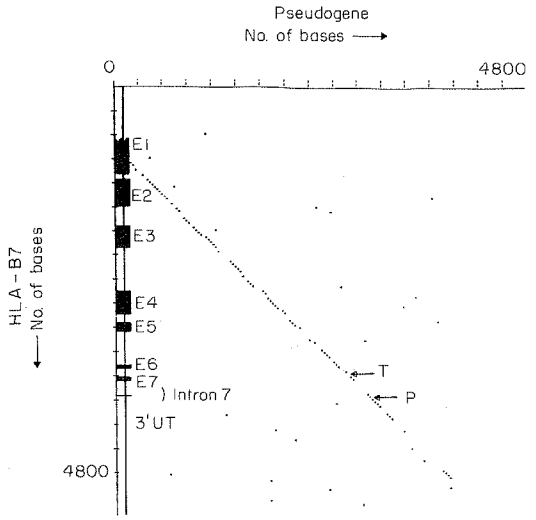
Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	"The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Map* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)

The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	 (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(p. 8101, Results) 

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	(p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)  (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants,

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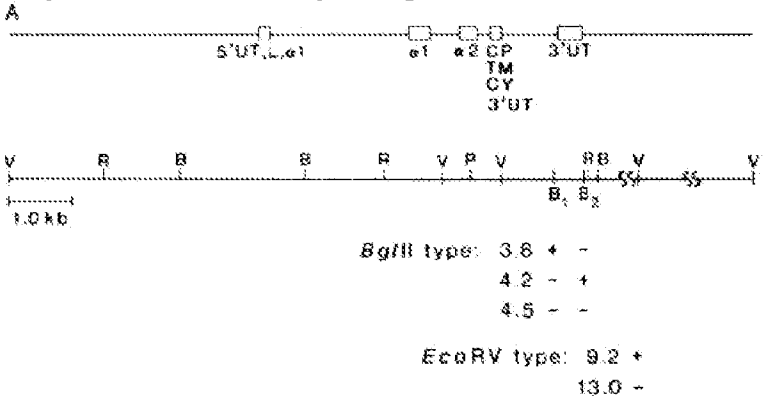
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(p. 8101, Results)  (p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)
Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)

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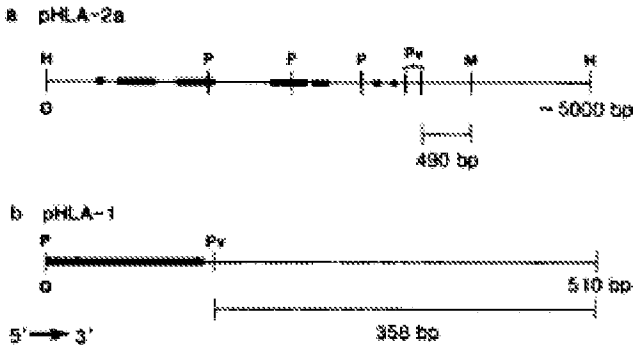
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	 FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
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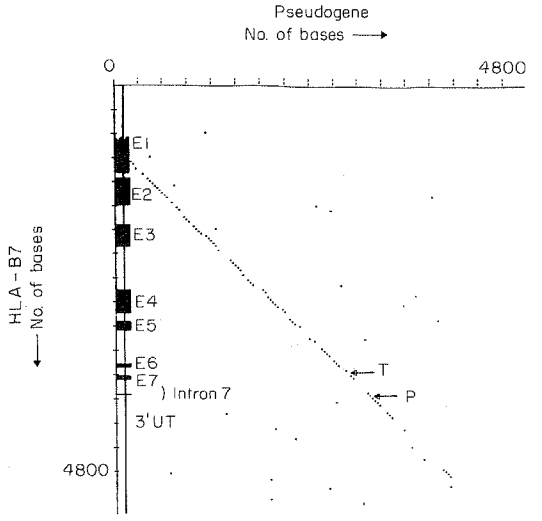
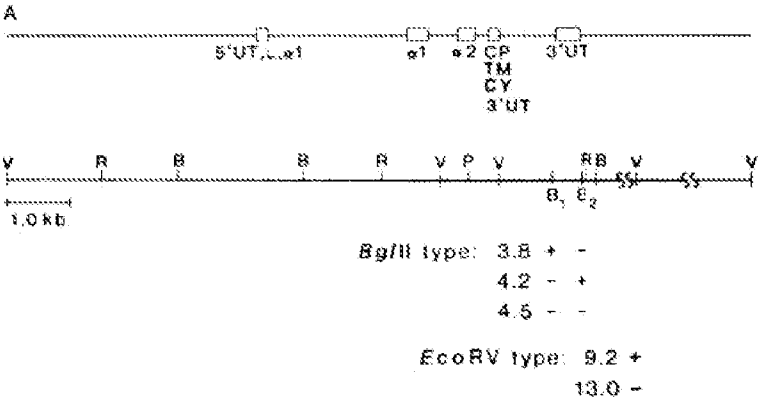
	 **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results) 

<table>
<tr><th colspan="2">Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)</th></tr>
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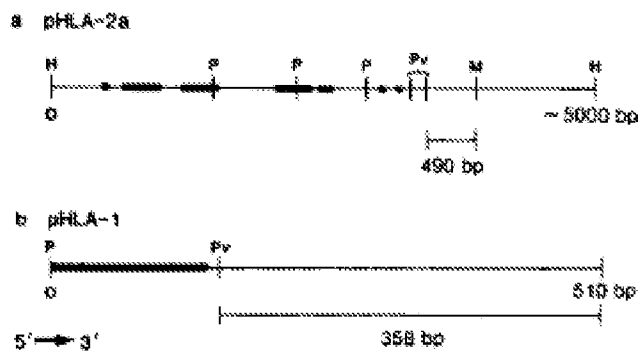
<tr><td></td><td>(p. 8102, bottom of page)

"The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)</td></tr>
<tr><td>Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.</td><td>Exhibit E teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)
 
FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (a), which encodes HLA-A2 from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (b) (19). Restriction endonuclease-cut sites indicated are H, HindIII; M, Msp I; P, Pst I; Pv, Pvu II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'.
(p. 5176, left column, bottom of page)

The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph)
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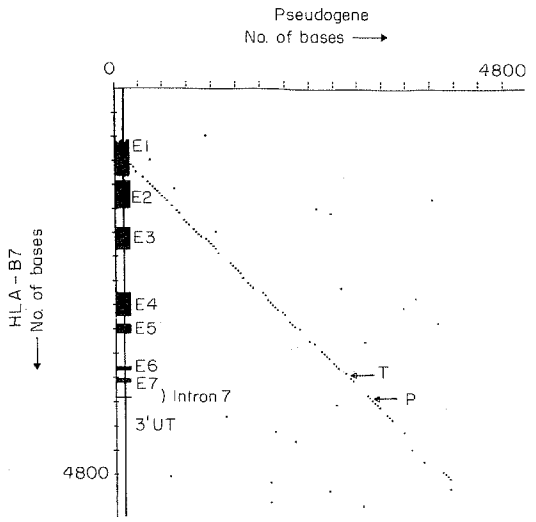
Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract) 
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	**Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results)

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
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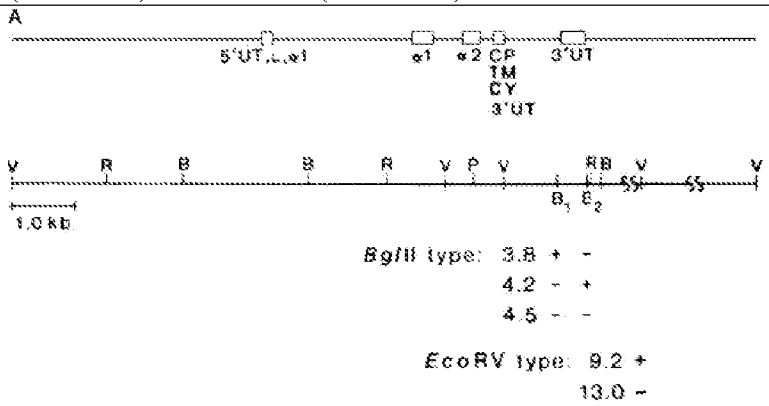
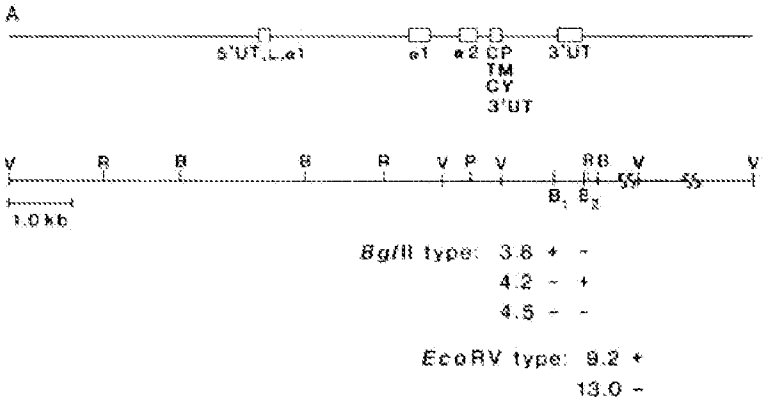
	 (p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2, located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph) **Exhibit F** teaches "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend) 

Obvious under 35 USC § 103(a): claims 26-32 are obvious over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	DiLella I (Exhibit A) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	(p. 8102, bottom of page)

Thus, it is respectfully requested that there be Reexamination of the '179 patent, with claims 26-32 rejected as being obvious under 35 USC § 103(a) over DiLella I (Exhibit A) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G).

5.2.2 Claims 26-32 are obvious over DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)

Exhibit B describes a DNA analysis method utilizing PCR that involves identifying a polymorphism or mutation in the PAH gene present in intron 12 and its association with a particular genetic haplotype. Exhibit E and G relate to HLA class I locus specific probes that provide information on polymorphisms in HLA class I genes and Exhibit F relates to HLA class II locus specific probes that provide information on polymorphisms in HLA class II genes. The motivation to combine these references can be found since all documents are related to the characterization of polymorphisms associated with genes having one or more allele. *See also* Section 5.1.2, *supra*, for support regarding Exhibit B. In view of all text before the following tables, all text herein concerning the Exhibits in the following tables, and the following tables, claims 26-32 are obvious in view of Exhibit B in view of Exhibits E, F and G; and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

Obvious under 35 USC § 103(a): claims 26-32 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
Claim 26. A DNA analysis method for determining coding region alleles of a multi-allelic genetic locus comprising	**Exhibit E** teaches Today, > 20 HLA-A and >40 HLA-B alleles have been described (p. 5175, left column, 1st paragraph) **Exhibit G** teaches "Use of the probe to analyze Southern

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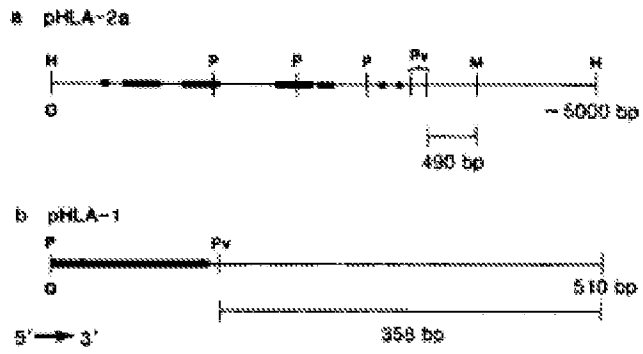
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	blots of genomic DNA from unrelated individuals provides the first direct demonstration of intragenic localization of an HLA allele-specific restriction endonuclease site." (See p. 501, abstract) **Exhibit F** teaches "To identify RFLPs associated with the HLA-DRa gene, genomic DNA from a variety of individuals was digested with nine different endonucleases, electrophoresed, and analyzed by blot hybridization with the pDRa-1 probe."(See p. 8101, Results)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Mlu* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) "The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction

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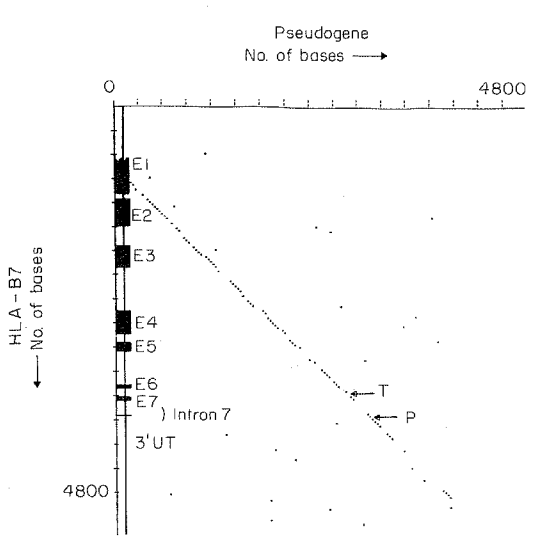
	and characterization of probes from the 3'-untranslated region that can circumvent these problems". (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)  (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results)

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	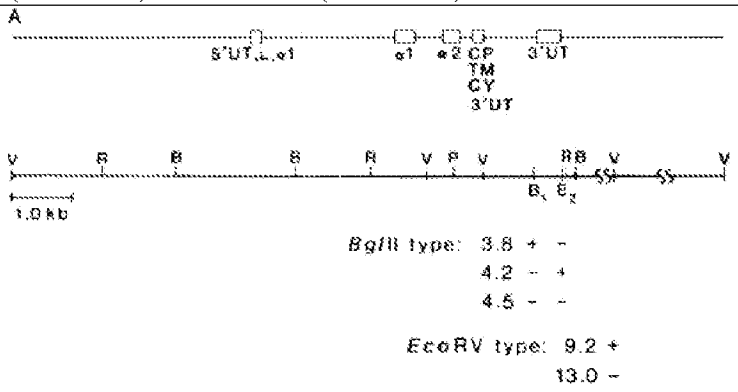 "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)

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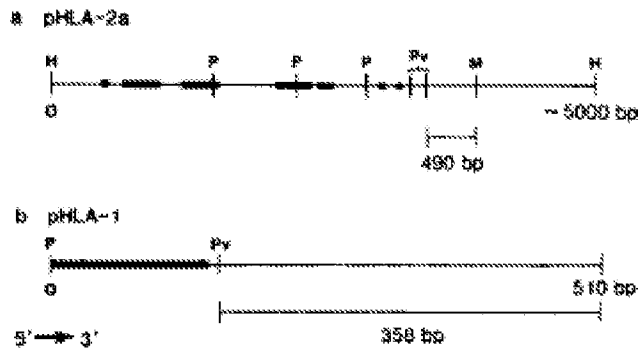
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)

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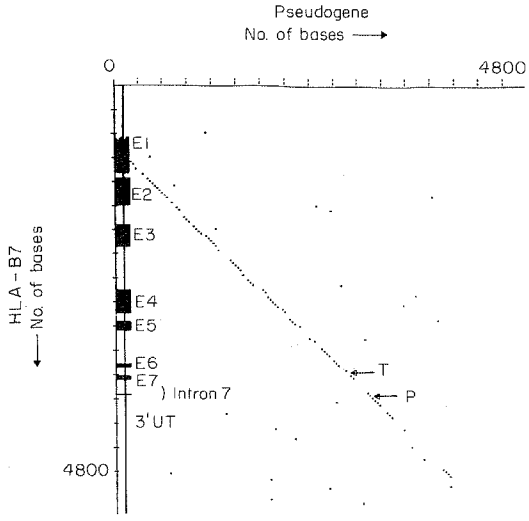
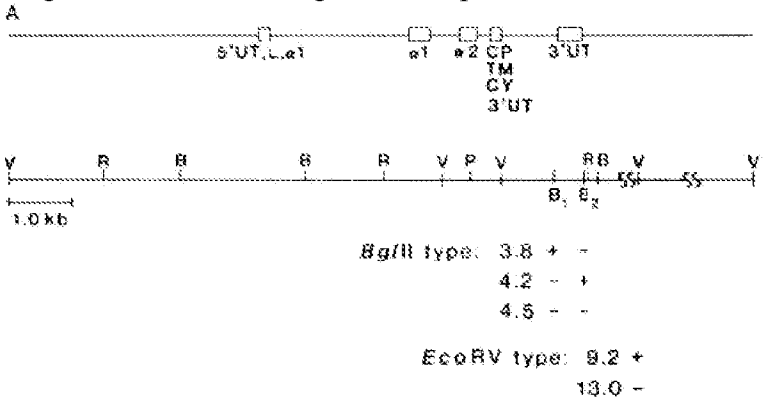
	 (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results) 

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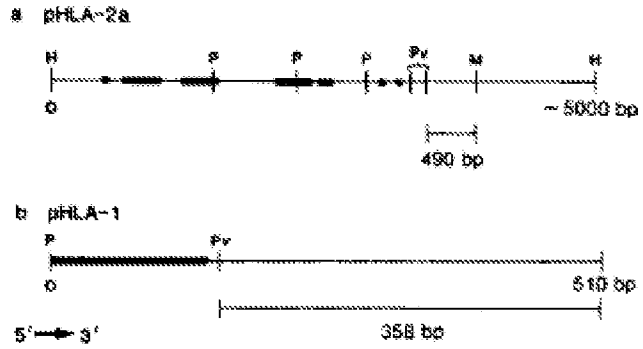
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult

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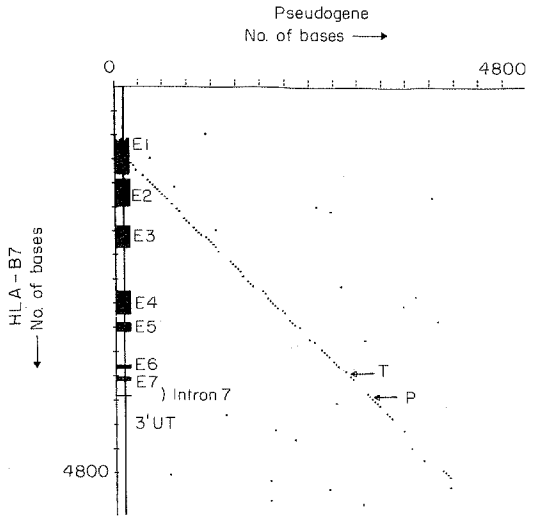
	to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)  (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants,

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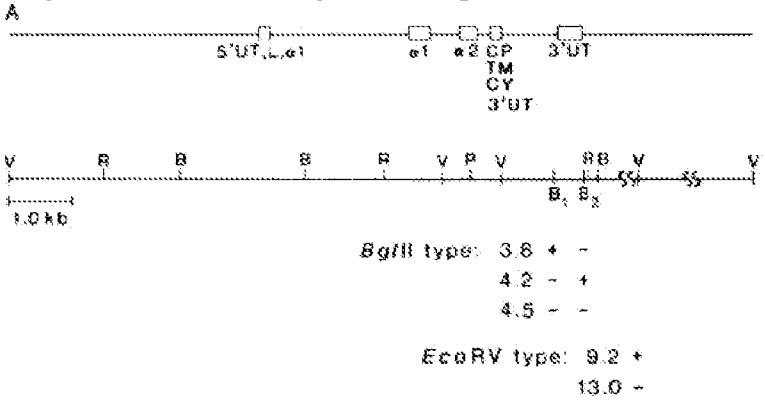
	homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results)  (p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)
Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)

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	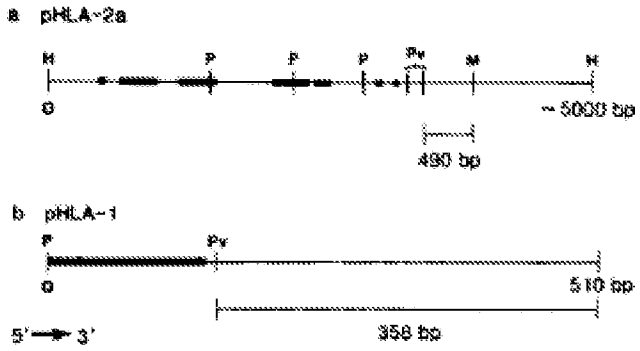 FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract)

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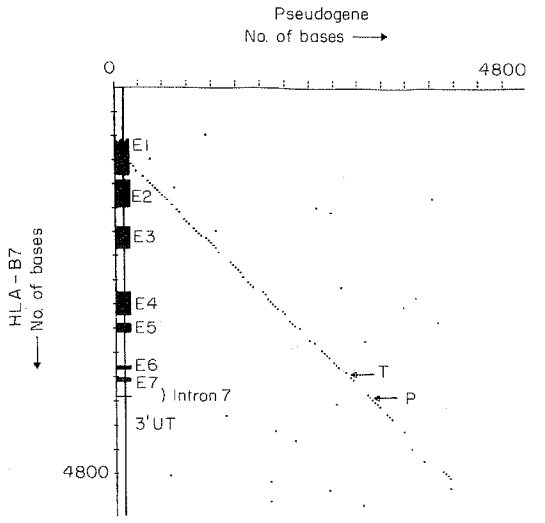
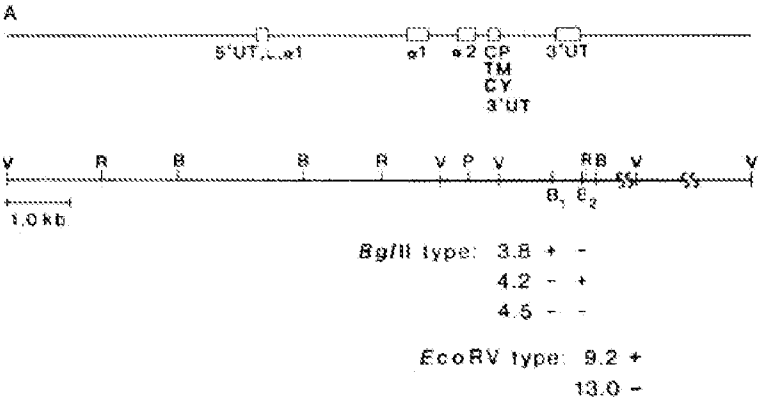
	 **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(p. 8101, Results) 

<table>
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<tr><td></td><td>(p. 8102, bottom of page)

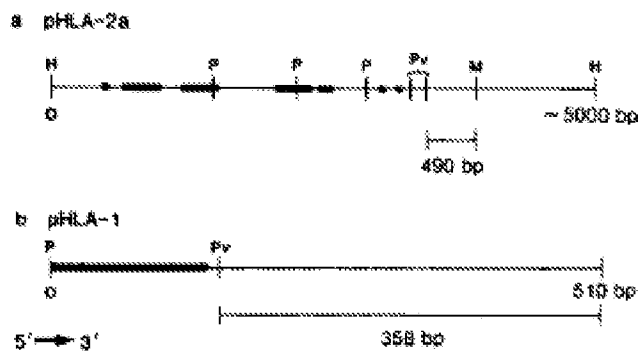
"The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)</td></tr>
<tr><td>Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.</td><td>Exhibit E teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)
 

FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (a), which encodes HLA-A2 from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (b) (19). Restriction endonuclease-cut sites indicated are H, HindIII; M, Msp I; P, Pst I; Pv, Pvu II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'.
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The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph)
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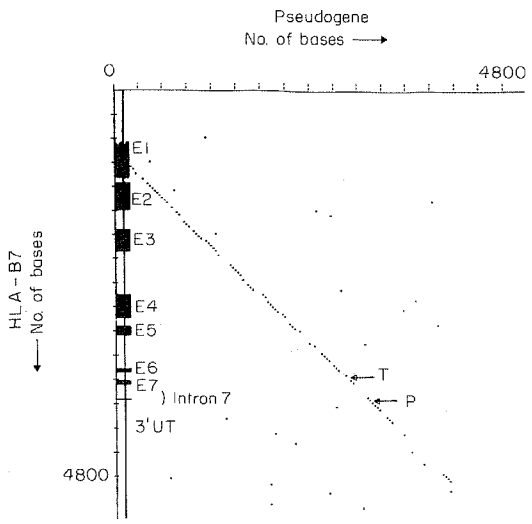
Obvious under 35 USC § 103(a): claims 26-32 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E), Stetler (Exhibit F) and Grumet (Exhibit G)
	locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (p. 501, abstract) 
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	**Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(p. 8101, Results)

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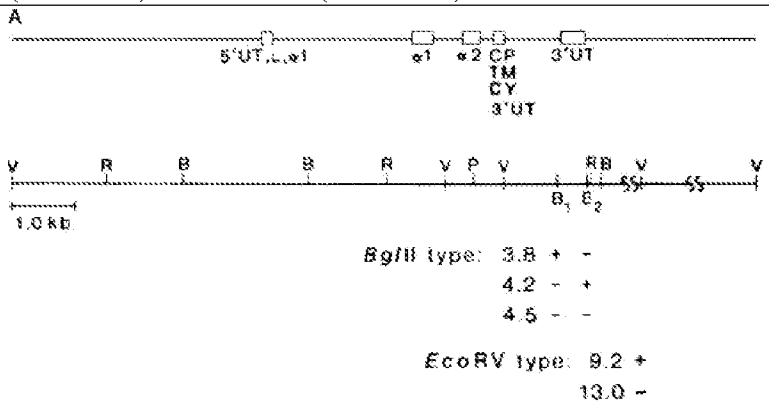
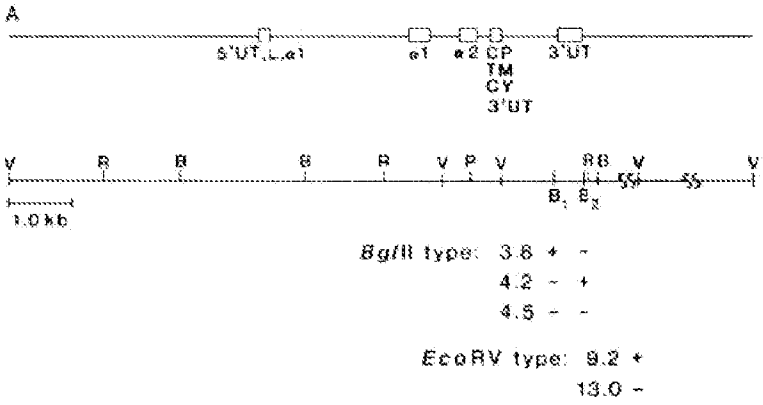
	 (p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2, located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend)
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph) **Exhibit F** teaches "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (p. 8102, Fig. 3 legend) 

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	(p. 8102, bottom of page)

5.2.3 Claims 26-32 are obvious over Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)

Exhibit C describes a DNA analysis method involving digestion with restriction endonucleases, southern blotting, hybridization and labeling with specific probes so as to characterize DNA polymorphisms associated with multiple haplotypes of the gene locus containing the genes A-1, C-III and A-IV. Exhibit D provides further information on a restriction fragment length polymorphism in the A-1 gene and indicates that non-coding DAN associated with the fragments generated is not more than two kilobases in length. Exhibit E and F relate to HLA class I locus specific probes that provide information on polymorphisms in HLA class I genes and Exhibit G relates to HLA class II locus specific probes that provide information on polymorphisms in HLA class II genes. The motivation to combine these references can be found since all documents are related to the characterization of polymorphisms associated with genes having one or more alleles. *See also* Section 5.1.3, *supra*, for support regarding Exhibit C. In view of all text before the following tables, all text herein concerning the Exhibits in the following tables, and the following tables, claims 26-32 are obvious in view of Exhibit C as evidenced by Exhibit D, in view of Exhibits E, F and G; and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

Obvious under 35 USC § 103(a): claims 26-32 are obvious over Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)
Claim 26. A DNA analysis method for determining coding region alleles of a multi-allelic	**Exhibit D** teaches "To date seven restriction fragment length polymorphisms (10-12) has been identified within the genes for apolipoproteins A-I, C-III, and A-IV which are located next to each

Obvious under 35 USC § 103(a): claims 26-32 are obvious over Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
The Simons '179 patent	Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)
genetic locus comprising	other within a 15 kb DNA fragment (13) (p. 132, left column, 2nd paragraph) and "The identification of an additional polymorphism within the apolipoprotein A-I/C-III/A-IV gene cluster, which we report here, makes this gene locus more informative for genetic analyses." (See p. 132, left column, 3rd paragraph) **Exhibit E** teaches Today, > 20 HLA-A and >40 HLA-B alleles have been described (p. 5175, left column, 1st paragraph) **Exhibit G** teaches "Use of the probe to analyze Southern blots of genomic DNA from unrelated individuals provides the first direct demonstration of intragenic localization of an HLA allele-specific restriction endonuclease site." (See p. 501, abstract) **Exhibit F** teaches "To identify RFLPs associated with the HLA-DRa gene, genomic DNA from a variety of individuals was digested with nine different endonucleases, electrophoresed, and analyzed by blot hybridization with the pDRa-1 probe."(See p. 8101, Results)
…identifying sequence polymorphisms characteristic of the alleles, wherein said sequence polymorphisms characteristic of the alleles are present in a non-coding region sequence, said non-coding region sequence being not more than about two kilobases in length.	**Exhibit D** teaches " Size comparison of the newly discovered Msp I fragment with a restriction map of the apolipoprotein A-I gene revealed that most likely the cutting site at the Y-end of the normally seen 673 bp fragment is lost giving rise to the observed 719 bp Msp I fragment." "Fig. 1 MSP I polymorphisms within the apolipoprotein A-I gene. The lower part shows a schematic drawing of the coding strand of the apolipoprotein A-I gene with boxes representing the exon sequences. The bar on top of the boxes indicates the length of the cDNA used for hybridization. Normal MspI cutting sites are indicated by arrows. The presence of all cutting sites leads to the detection of 0.67 kb and 1.08 kb MspI fragments (allele A1). If the MspI site within intron 3 (IVS 3) is absent, a 1.76 kb fragment is generated (allele A2). The absence of the MspI site within intron 1 creates a 0.72 kb polymorphic fragment (allele A3). (p. 133, left column, 1st paragraph)

Obvious under 35 USC § 103(a): claims 26-32 are obvious over Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)	
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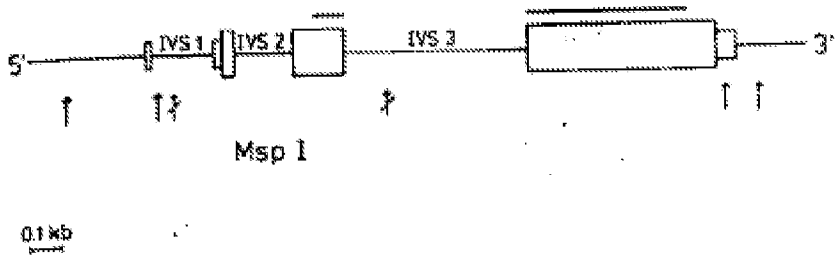
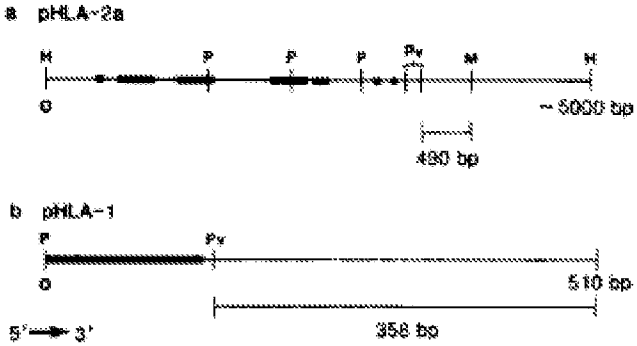
	 **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)  FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) "The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems". (p. 5177, right column, 3rd paragraph)

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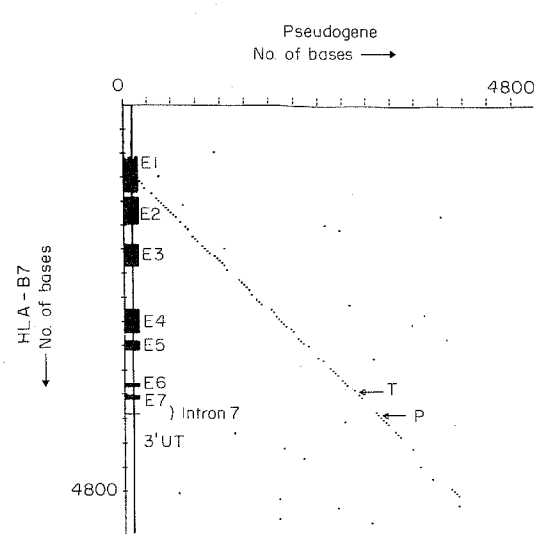
	Exhibit G teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)  (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results)

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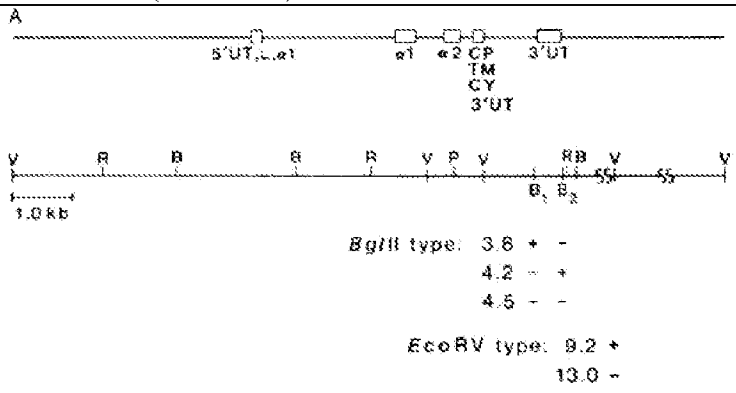
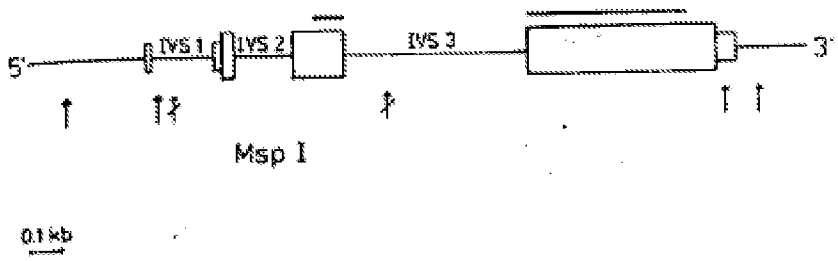
	 "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)
Claim 27. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within five kilobases of a variable exon of the genetic locus.	**Exhibit D** teaches "Fig. 1 MSP I polymorphisms within the apolipoprotein A-I gene. The lower part shows a schematic drawing of the coding strand of the apolipoprotein A-I gene with boxes representing the exon sequences. The bar on top of the boxes indicates the length of the cDNA used for hybridization. Normal MspI cutting sites are indicated by arrows. The presence of all cutting sites leads to the detection of 0.67 kb and 1.08 kb MspI fragments (allele A1). If the MspI site within intron 3 (IVS 3) is absent, a 1.76 kb fragment is generated (allele A2). The absence of the MspI site within intron 1 creates a 0.72 kb polymorphic fragment (allele A3)." (p. 133, left column, 1st paragraph)  **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)

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	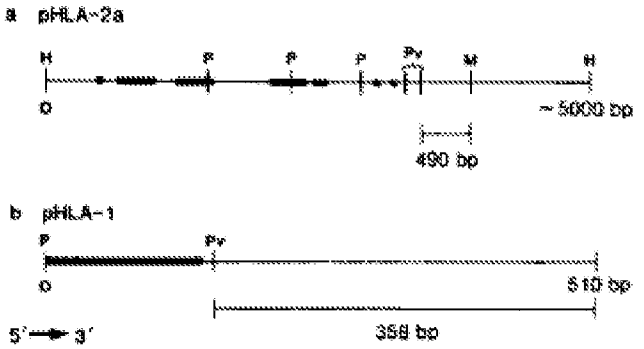 FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)

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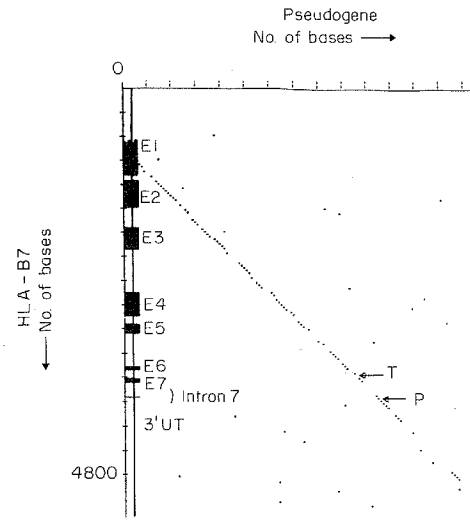
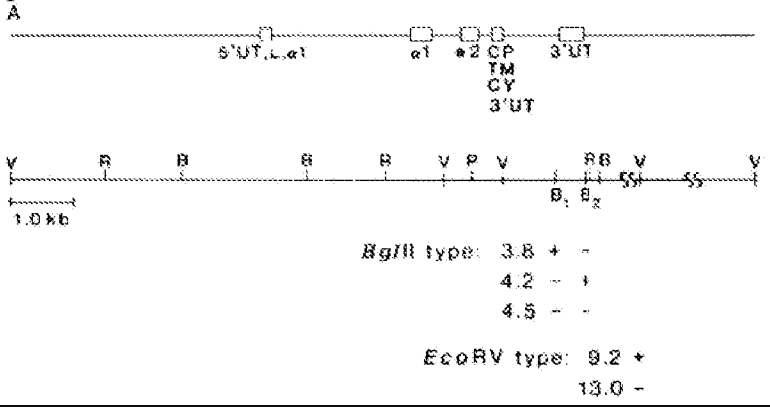
	 (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results) 

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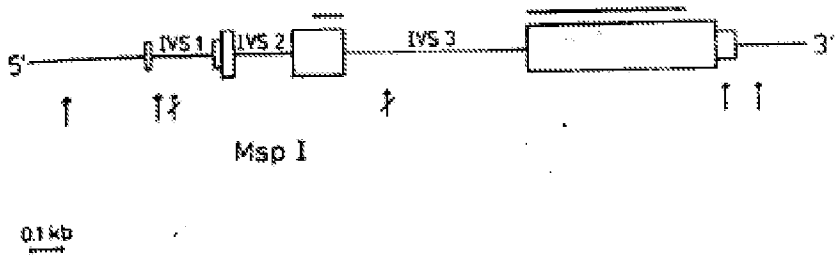
Claim 28. The method of claim 26 wherein said sequence polymorphisms characteristic of the alleles are within two kilobases of a variable exon of the genetic locus.	**Exhibit D** teaches "Fig. 1 MSP I polymorphisms within the apolipoprotein A-I gene. The lower part shows a schematic drawing of the coding strand of the apolipoprotein A-I gene with boxes representing the exon sequences. The bar on top of the boxes indicates the length of the cDNA used for hybridization. Normal MspI cutting sites are indicated by arrows. The presence of all cutting sites leads to the detection of 0.67 kb and 1.08 kb MspI fragments (allele A1). If the MspI site within intron 3 (IVS 3) is absent, a 1.76 kb fragment is generated (allele A2). The absence of the MspI site within intron 1 creates a 0.72 kb polymorphic fragment (allele A3)." (p. 133, left column, 1st paragraph)  **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)

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	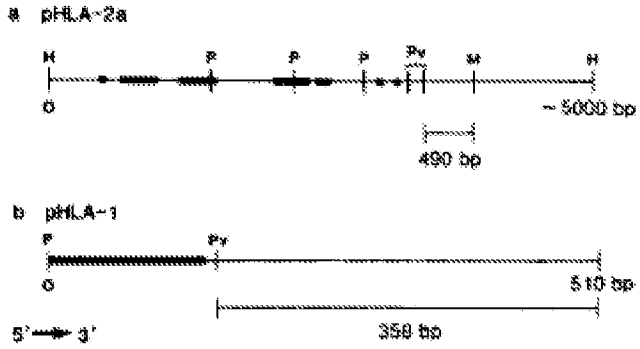 FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)

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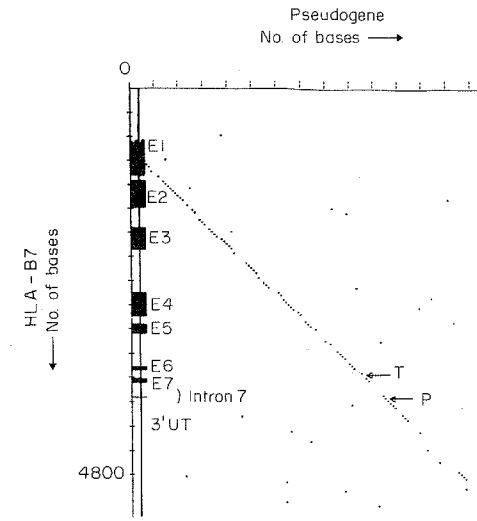
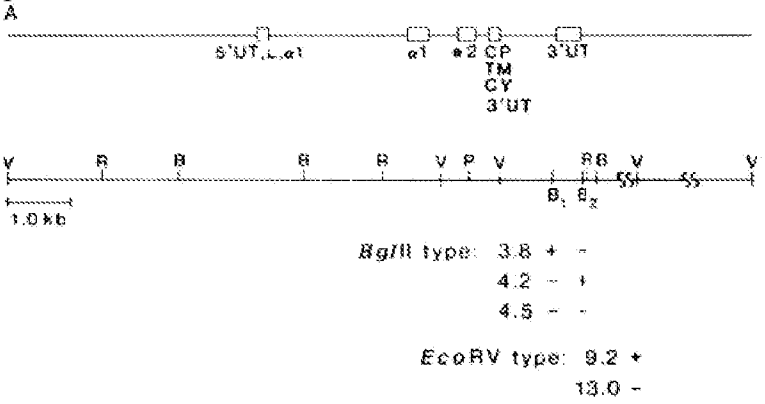
	 (see p. 504, top of page) **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results) 

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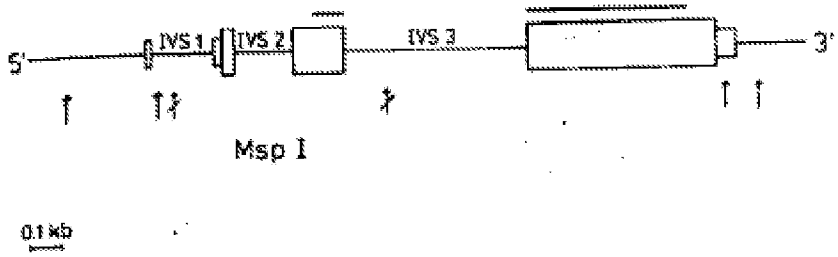
"The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)</td></tr>
<tr><td>Claim 29. The method of claim 26 wherein said sequence polymorphism characteristic of said coding region allele is present in an intervening sequence adjacent to a variable exon of the locus.</td><td>Exhibit D teaches "Fig. 1 MSP I polymorphisms within the apolipoprotein A-I gene. The lower part shows a schematic drawing of the coding strand of the apolipoprotein A-I gene with boxes representing the exon sequences. The bar on top of the boxes indicates the length of the cDNA used for hybridization. Normal MspI cutting sites are indicated by arrows. The presence of all cutting sites leads to the detection of 0.67 kb and 1.08 kb MspI fragments (allele A1). If the MspI site within intron 3 (IVS 3) is absent, a 1.76 kb fragment is generated (allele A2). The absence of the MspI site within intron 1 creates a 0.72 kb polymorphic fragment (allele A3)". (p. 133, left column, 1st paragraph)
 

Exhibit E teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)</td></tr>
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	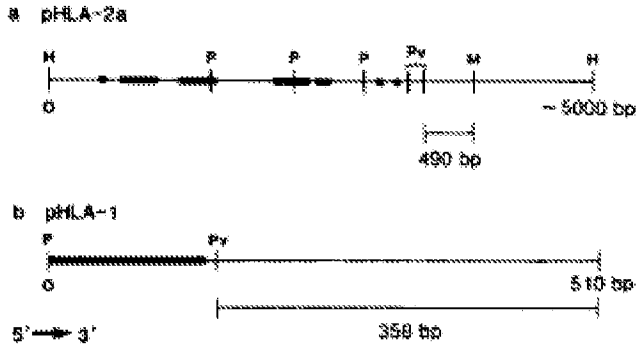 FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (*a*), which encodes *HLA-A2* from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (*b*) (19). Restriction endonuclease-cut sites indicated are H, *Hin*dIII; M, *Msp* I; P, *Pst* I; Pv, *Pvu* II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'. (p. 5176, left column, bottom of page) The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph) **Exhibit G** teaches "A DNA probe specific for the HLA-B locus has been isolated from a broadly cross-reactive HLA class I genomic clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract)

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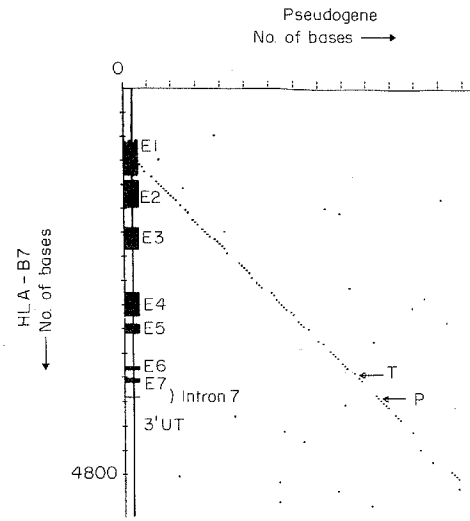
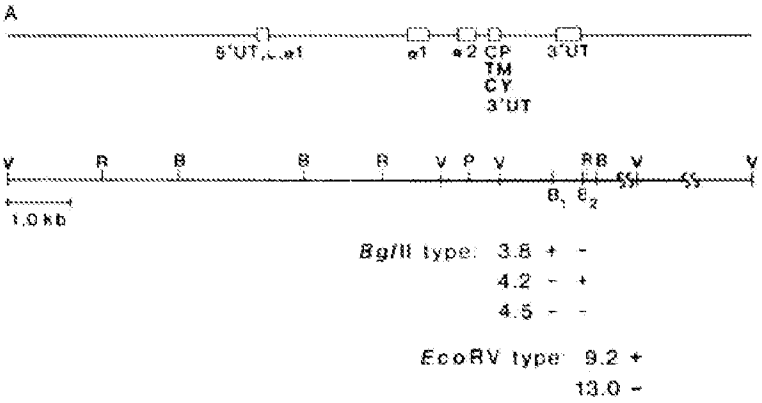
	 **Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results) 

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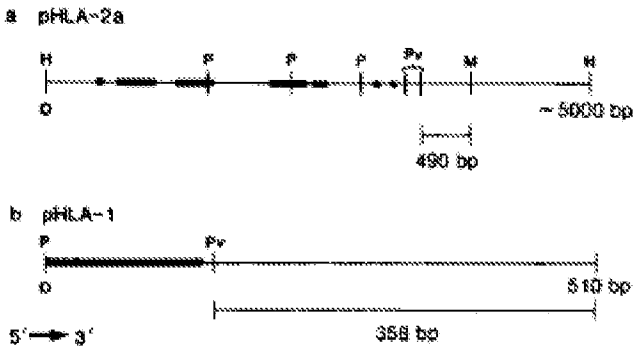
"The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2,located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)</td></tr>
<tr><td>Claim 30. The method of claim 29 wherein the genetic locus is an HLA Class I locus and the intervening sequence is intervening sequence I, II or III.</td><td>Exhibit E teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721"(p. 5175, right column, 4th paragraph)
 

FIG. 1. Localization of subclones used as locus-specific probes from the genomic clone pHLA-2a (a), which encodes HLA-A2 from LCL 721 (unpublished data), and from the HLA class I cDNA clone pHLA-1 (b) (19). Restriction endonuclease-cut sites indicated are H, HindIII; M, Msp I; P, Pst I; Pv, Pvu II. Coding regions of each clone are indicated by solid boxes. Both clones are depicted 5' → 3'.
(p. 5176, left column, bottom of page)

The HLA-A and –B genes are part of a multigene family with >15 members (13-15). The high level of sequence conservation within the class I family has made it difficult to use class I cDNA probes containing coding information to identify and study the products of any given class I locus independent of other family members, at either the RNA or DNA level. This paper describes the construction and characterization of probes from the 3'-untranslated region that can circumvent these problems. (p. 5177, right column, 3rd paragraph)
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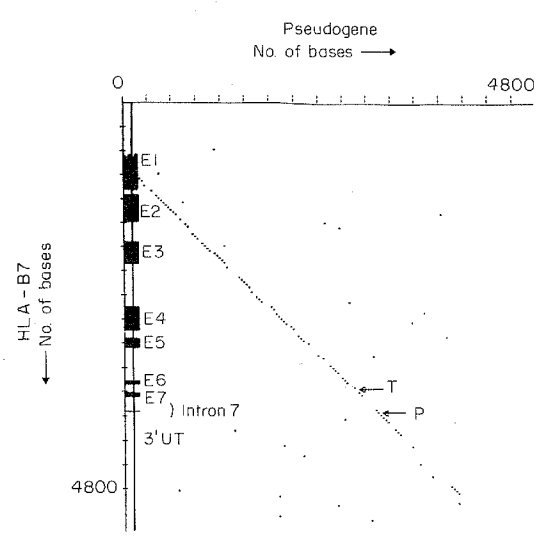
	clone. Locus specificity of the probe appears to be derived primarily from a stretch of approximately 180 nucleotides comprising the last (7th) intron of the original B7 gene." (See p. 501, abstract) 
Claim 31. The method of claim 29 wherein the genetic locus is an HLA Class II locus and the intervening sequence is intervening sequence I or II.	**Exhibit F** teaches "The number of different individual DNAs tested by a given restriction endonuclease varied from 2 to 10. The enzymes HindIII, EcoRI, Kpn I, Msp I, Xho I, Pst I, and Pvu II failed to reveal any RFLPs, but digestion with Bgl II and EcoRV revealed the presence of three polymorphic restriction fragments [3:8 kilobase pairs (kb), 4.2 kb, and 4.5 kb] and two polymorphic restriction fragments (9.2 kb and 13.0 kb), respectively. The genomic-blotting analysis of HLA deletion variants, homozygous typing cells, and families indicated that each polymorphic fragment length represents an allele of the single-locus HLA-DRα gene."(See p. 8101, Results)

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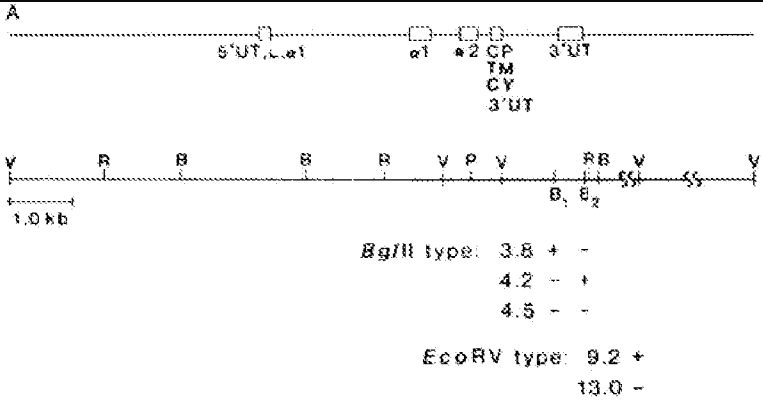
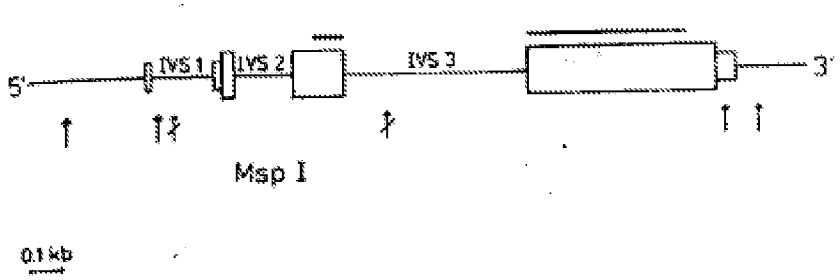
	 (p. 8102, bottom of page) "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2, located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)
Claim 32. The method of claim 26 wherein said non-coding region sequence is not more than about one kilobase in length.	**Exhibit D** teaches "Fig. 1 MSP I polymorphisms within the apolipoprotein A-I gene. The lower part shows a schematic drawing of the coding strand of the apolipoprotein A-I gene with boxes representing the exon sequences. The bar on top of the boxes indicates the length of the cDNA used for hybridization. Normal MspI cutting sites are indicated by arrows. The presence of all cutting sites leads to the detection of 0.67 kb and 1.08 kb MspI fragments (allele A1). If the MspI site within intron 3 (IVS 3) is absent, a 1.76 kb fragment is generated (allele A2). The absence of the MspI site within intron 1 creates a 0.72 kb polymorphic fragment (allele A3)." (p. 133, left column, 1st paragraph)  **Exhibit E** teaches "In this report, we describe probes isolated from

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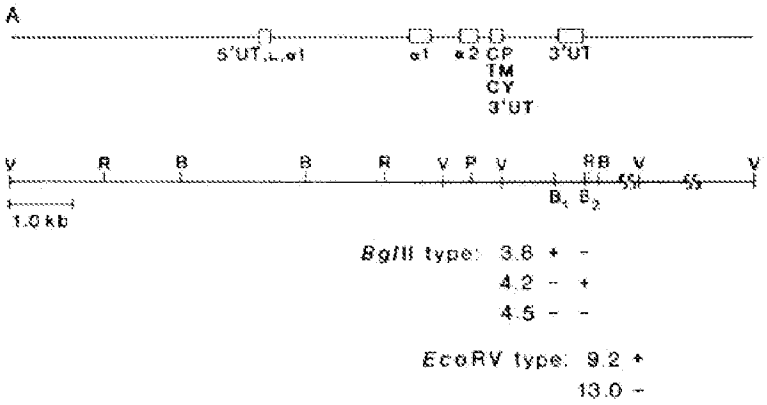
The Simons '179 patent	Paul (Exhibit C) as evidenced by Funke (Exhibit D) in view of Koller (Exhibit E), in view of Stetler (Exhibit F) and in further view of Grumet (Exhibit G)
	the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph) **Exhibit F** teaches "The polymorphic Bgl II sites B1, located within an intron 41 bp from the start of the 3'UT exon, and B2, located 9 bp 3' of the polyadenylylation original, are expanded" (See p. 8102, Fig. 3 legend)  (p. 8102, bottom of page)

5.2.4 Claims 1-18 are obvious over DiLella II (Exhibit B) in view of Koller (Exhibit E) and Stetler (Exhibit F) (or claims 1-18 are obvious in view of Exhibit B in view of Exhibits E, F, I.4 and I.5[9])

Exhibit B describes a DNA analysis method utilizing PCR that involves identifying a polymorphism or mutation in the PAH gene present in intron 12 and its association with a particular genetic haplotype. Mutations in the PAH gene are responsible PKU which is a characteristic monogenic disease and one of the commonest inherited disorders. More than 500 different PAH alleles have been recorded in the PAH database as stated in Exhibit I.5. Exhibit E

[9] While Exhibits I.4 and I.5 are provided to demonstrate evidence of universal facts, *cf.* MPEP 2131.01, to any extent they needs to be included in a rejection or statement of SNQ, they are so included in the parenthetical. More than one reference can be employed in an anticipation rejection when the second reference is cited for evidence of a universal fact; and, references for demonstrating universal facts need not be before any filing date of the '179 patent. *See* §§ MPEP 2131.01; 2124.

relates to HLA class I locus specific probes that provide information on polymorphisms in HLA class I genes and Exhibit F relates to HLA class II locus specific probes that provide information on polymorphisms in HLA class II genes. The motivation to combine these references can be found since all documents are related to the characterization of polymorphisms associated with genes having one or more allele. *See also* Sections 5.1.2 and 5.2, *supra*, for support regarding Exhibit B, and Exhibits B, E, and F, and Exhibits B, E, F, I.4 and I.5. Based on the text herein, including all the text before the following tables, all text herein concerning the Exhibits in the following tables, and the following tables, claims 1-18 are obvious in view of Exhibit B in view of Exhibits E and F; or, claims 1-18 are obvious in view of Exhibit B in view of Exhibits E, F, I.4 and I.5; and reexamination based thereon, with a resultant reexamination certificate cancelling these claims, are respectfully requested.

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 1. A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising:….	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
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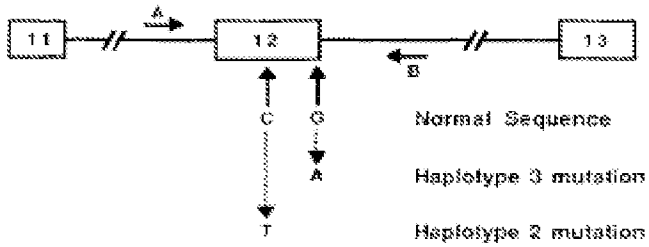
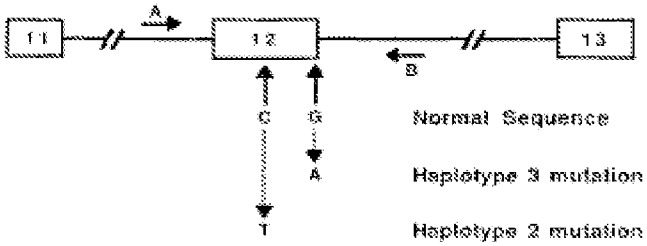
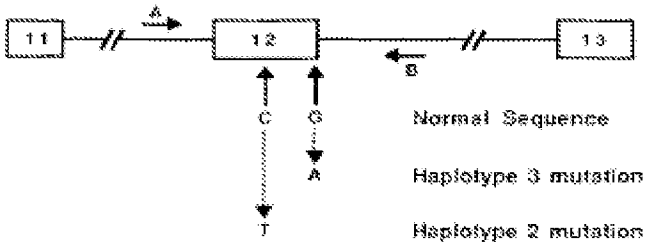
…..a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and ….	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) "Twelve restriction fragment length polymorphism (RFLP) haplotypes at the PAH locus in the northern European population have been characterised, and about 90% of the PKU alleles in this population are confined to RFLP haplotypes 1-4. Different combinations of the mutant RFLP haplotypes contribute to the allelic and clinical diversity of PKU." (p. 497) "The mutation associated with haplotype 3 is caused by a substitution at amino acidresidue 408 in exon 12/intron 12 boundary and comprises about 40% of mutant alleles…" (p. 497) "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig1)." (p. 498)  **Exhibit F** teaches "The observed correlations of *DRα Bgl* II restriction site variants with serologically determined DR specificities suggest linkage disequilibrium between the DRα and the DRβ loci.

…b) analyzing the amplified DNA sequence to detect the allele.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry;" (Summary) "The mutation associated with haplotype 3 is caused by a single base substitution at the exon 12/ intron 12 boundary…" (p. 497) **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721" (p. 5175, right column, 4th paragraph)
Claim 2. The method of claim 1 wherein said amplified DNA sequence includes at least about 300 nucleotides corresponding to non-coding region sequences.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig1)." (p. 498) "Fig 1- Schematic representation of 245 bp DNA fragment containing exon 12 and flanking intronic sequences of PAH gene." (p. 498) 
Claim 3. The method of claim 1 wherein said non-coding region sequence is adjacent to an exon encoding said allele.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig 1)." 

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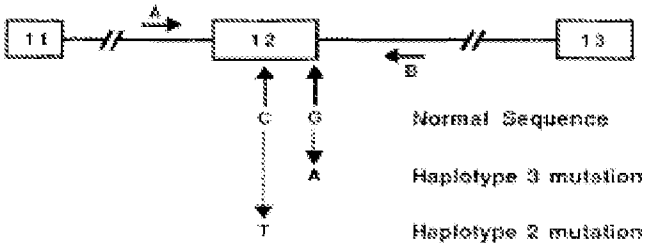
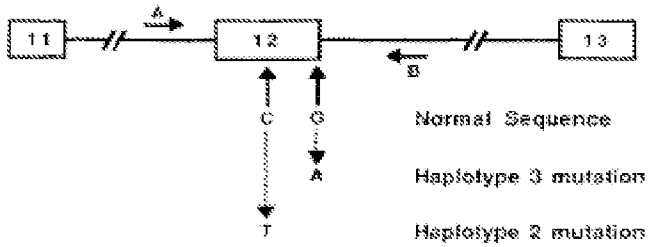
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 4. The method of claim 1 wherein said amplified DNA sequence is characteristic of at least one nonadjacent allele.	**Exhibit B** teaches "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig 1)." 
Claim 5. The method of claim 1 wherein said amplified DNA sequence is characteristic of at least one adjacent allele and at least one nonadjacent allele.	**Exhibit B** teaches that the single base substitution is at the exon/12/intron 12 boundary (specifically at the 5' donor splice site of intron 12 as mentioned in Exhibit A). Intron 12 is an intervening sequence which is adjacent to exon 12.
Claim 6. The method of claim 5 wherein said amplified DNA sequence includes at least about 1,000 nucleotides corresponding to non-coding region sequences.	**Exhibit E** teaches "Probes. An *HLA-B* locus-specific probe, pHLA-1.1 (Fig. 1b), was prepared by digesting cDNA clone pHLA-l (22) with restriction endonucleases *Pvu* II and *Pst* I. The DNA digest was subjected to electrophoresis in a 5% acrylamide gel. A 358-base-pair (bp) fragment was isolated from the acrylamide gel according to Maxam and Gilbert (23). This fragment contains only 3'-untranslated sequences and does not include the poly(A) tail or poly(A) addition site. An HLA-A locus-specific probe, pHLA-2a.l, was prepared from the HLA-A2 genomic clone pHLA-2a (Fig. la). A 490 bp *Pvu* II-*Msp* I fragment of pHLA-2a was subcloned into the *Ace* I and *Sma* I sites of pUC9 (24). By sequence analysis, this subclone contains most of the HLA-A2 3'-untranslated region and 72 bp of 3/-flanking DNA. The 490-bp insert was isolated as described above (23)." (p.5176, left column, 2nd paragraph)
Claim 7. The method of claim 1 wherein said genetic locus has at least four alleles.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
	patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)
Claim 8. The method of claim 1 wherein said genetic locus has at least eight alleles.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)
Claim 9. A method for detection of at least one allele of a multi-allelic genetic locus comprising: …..	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
…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 allele and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and…	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) "Twelve restriction fragment length polymorphism (RFLP) haplotypes at the PAH locus in the northern European population have been characterised, and about 90% of the PKU alleles in this population are confined to RFLP haplotypes 1-4. Different combinations of the mutant RFLP haplotypes contribute to the allelic and clinical diversity of PKU." (p. 497) "The mutation associated with haplotype 3 is caused by a substitution at amino acidresidue 408 in exon 12/intron 12 boundary and comprises about 40% of mutant alleles…" (p. 497) "The specific amplification of a 245 base pair (bp) region containing exon 12 and the flanking intronic sequences was attempted with oligonucleotides A and B as primers because this region contains both haplotype 2 and 3 mutation sites (fig1)." (p. 498)  **Exhibit F** teaches "The observed correlations of *DRα Bgl* II restriction site variants with serologically determined DR specificities suggest linkage disequilibrium between the DRα and the DRβ loci.

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
…b) analyzing said amplified DNA sequence to determine the presence of a genetic variation in said amplified sequence to detect the allele.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry;" (Summary) "The mutation associated with haplotype 3 is caused by a single base substitution at the exon 12/ intron 12 boundary…" (p. 497) **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721, demonstrating that locus specific sequences can be identified for members of the class I multigene family" (p. 5175, right column, 4th paragraph)
Claim 10. The method of claim 9 wherein said variation in said amplified DNA sequence is a variation in the length of the primer-defined amplified DNA sequence.	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) **Exhibit F** teaches "Use of Polymorphic Restriction Sites as Genetic Markers. Table 1 shows the frequency of the *Bgl* II and *Eco*RV alleles separately as well as that of *Bgl* II/*Eco*RV haplotypes in a small panel of homozygous typing cells (nine cell lines) and a larger population of unrelated control individuals. The *Bgl* II 3.8-kb, *Eco*RV 13.0-kb type and the *Bgl* II 4.2-kb, *Eco*RV 9.2-kb type are more frequent than would be expected assuming random association, demonstrating that these combinations of alleles are in positive linkage disequilibrium. Similarly, the *Bgl* II 3.8-kb, *Eco*RV 9.2-kb type and the *Bgl* II 4.2-kb, EcoRV 13.0-kb type are less frequent than would be expected by random association." (p. 8101, right column, 3rd paragraph)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 11. The method of claim 9 wherein said variation in said amplified DNA sequence is a change in the presence of at least one restriction site in the primer-defined amplified DNA sequence.	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) **Exhibit F** teaches "Use of Polymorphic Restriction Sites as Genetic Markers. Table 1 shows the frequency of the *Bgl* II and *Eco*RV alleles separately as well as that of *Bgl* II/*Eco*RV haplotypes in a small panel of homozygous typing cells (nine cell lines) and a larger population of unrelated control individuals. The *Bgl* II 3.8-kb, *Eco*RV 13.0-kb type and the *Bgl* II 4.2-kb, *Eco*RV 9.2-kb type are more frequent than would be expected assuming random association, demonstrating that these combinations of alleles are in positive linkage disequilibrium. Similarly, the *Bgl* II 3.8-kb, *Eco*RV 9.2-kb type and the *Bgl* II 4.2-kb, EcoRV 13.0-kb type are less frequent than would be expected by random association." (p. 8101, right column, 3rd paragraph)
Claim 12. The method of claim 9 wherein said variation in said amplified DNA sequence is a change in the location of at least one restriction site in the primer-defined amplified DNA sequence.	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) **Exhibit F** teaches "Use of Polymorphic Restriction Sites as Genetic Markers. Table 1 shows the frequency of the *Bgl* II and *Eco*RV alleles separately as well as that of *Bgl* II/*Eco*RV haplotypes in a small panel of homozygous typing cells (nine cell lines) and a larger population of unrelated control individuals. The *Bgl* II 3.8-kb, *Eco*RV 13.0-kb type and the *Bgl* II 4.2-kb, *Eco*RV 9.2-kb type are more frequent than would be expected assuming random association, demonstrating that these combinations of alleles are in positive linkage disequilibrium. Similarly, the *Bgl* II 3.8-kb, *Eco*RV 9.2-kb type and the *Bgl* II 4.2-kb, EcoRV 13.0-kb type are less frequent than would be expected by random association." (p. 8101, right column, 3rd paragraph)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 13. The method of claim 9 wherein said variation in said amplified DNA sequence is a substitution of at least one nucleotide in the primer-defined amplified DNA sequence.	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) **Exhibit F** teaches "Use of Polymorphic Restriction Sites as Genetic Markers. Table 1 shows the frequency of the *Bgl* II and *Eco*RV alleles separately as well as that of *Bgl* II/*Eco*RV haplotypes in a small panel of homozygous typing cells (nine cell lines) and a larger population of unrelated control individuals. The *Bgl* II 3.8-kb, *Eco*RV 13.0-kb type and the *Bgl* II 4.2-kb, *Eco*RV 9.2-kb type are more frequent than would be expected assuming random association, demonstrating that these combinations of alleles are in positive linkage disequilibrium. Similarly, the *Bgl* II 3.8-kb, *Eco*RV 9.2-kb type and the *Bgl* II 4.2-kb, EcoRV 13.0-kb type are less frequent than would be expected by random association." (p. 8101, right column, 3rd paragraph)
Claim 14. The method of claim 9 wherein said genetic locus is a major histocompatibility locus.	**Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721, demonstrating that locus specific sequences can be identified for members of the class I multigene family" (p. 5175, right column, 4th paragraph)
Claim 15. The method of claim 9 wherein said allele is associated with a monogenic disease.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 16. The method of claim 15 wherein said monogenic disease is cystic fibrosis.	**Exhibit B** teaches "Single base substitutions have been identified in two mutant phenylalanine hydroxylase (PAH) alleles that cause phenylketonuria (PKU). The two mutant alleles are common among Caucasians of northern European ancestry; detection in genomic DNA samples of patients and carriers by hybridization with oligonucleotides specific for the respective mutant alleles requires fractionation of restriction-enzyme-digested genomic DNA samples by gel electrophoresis. This method is too cumbersome for mass screening. Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary)
Claim 17. The method of claim 9 wherein at least about 70% of said primer-defined amplified DNA sequence corresponds to non-coding region sequences.	**Exhibit B** teaches "Identification of carriers of the mutant alleles was achieved by direct analysis of their genomic DNA samples after specific amplification of a sub-genomic DNA fragment containing both mutation sites by polymerase chain reaction." (Summary) **Exhibit E** teaches "In this report, we describe probes isolated from the 3'-untranslated region of HLA-A and –B genes that, under high-stringency conditions, hybridize only to one locus in LCL 721, demonstrating that locus specific sequences can be identified for members of the class I multigene family" (p. 5175, right column, 4th paragraph) "This fragment contains only 3'-untranslated sequences and does not include the poly(A) tail or poly(A) addition site." (p.5176, left column, 2nd paragraph)

Obvious under 35 USC § 103(a): claims 1-18 are obvious in view of DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)	
The Simons '179 patent	DiLella II (Exhibit B) in view of Koller (Exhibit E) and in view of Stetler (Exhibit F)
Claim 18. The method of claim 9 wherein said primer-defined amplified DNA sequence is from 300 to 500 nucleotides in length.	**Exhibit E** teaches "Probes. An *HLA-B* locus-specific probe, pHLA-1.1 (Fig. 1b), was prepared by digesting cDNA clone pHLA-l (22) with restriction endonucleases *Pvu* II and *Pst* I. The DNA digest was subjected to electrophoresis in a 5% acrylamide gel. A 358-base-pair (bp) fragment was isolated from the acrylamide gel according to Maxam and Gilbert (23). This fragment contains only 3'-untranslated sequences and does not include the poly(A) tail or poly(A) addition site. An HLA-A locus-specific probe, pHLA-2a.l, was prepared from the HLA-A2 genomic clone pHLA-2a (Fig. la). A 490 bp *Pvu* II-*Msp* I fragment of pHLA-2a was subcloned into the *Ace* I and *Sma* I sites of pUC9 (24). By sequence analysis, this subclone contains most of the HLA-A2 3'-untranslated region and 72 bp of 3/-flanking DNA. The 490-bp insert was isolated as described above (23)." (p.5176, left column, 2nd paragraph)

5.2.5 Claims 1-18 and 26-32 are obvious over or anticipated by EP469 (Exhibit H) (or claims 1-18 and 26-32 are obvious or anticipated by Exhibit H and Exhibit I.3[10])

As especially discussed in Section 3.3, Claims 1-18 and 26-32 are not supported by the specification of the '179 patent, or any application in the lineage of the '179 patent, and are entitled to only a filing date of September 23, 1992.

EP469 (Exhibit H) corresponds to the '179 patent and was published February 27, 1991 and is available under 35 U.S.C § 102 (b) against claims 1-18 26-32 for use in obviousness and anticipation rejections of those claims.

At the very least, claims 1-18 and 26-32 are suggested by EP469 (or Exhibit H in view of Exhibit I.3). EP469 relates to the subject matter of claims 1-18 and 26-32 of the '179 patent. (Exhibit I.3 as discussed throughout this document, is cited for demonstration of a universal fact

[10] While Exhibit I.3 is provided to demonstrate evidence of a universal fact, *cf.* MPEP 2131.01, to any extent it needs to be included in a rejection or statement of SNQ, it is so included in the parenthetical. More than one reference can be employed in an anticipation rejection when the second reference is cited for evidence of a universal fact. *See* MPEP § 2131.01.

as to the meaning of "multi" and hence how "multi-allelic" and "multi-allelic genetic locus" render claims 1-18 and 26-32 as entitled to only the September 23, 1992 actual filing date of the '179 patent.)

Indeed, what patentee has relied upon for "support" when it has had Section 112 issues in the original examination are admissions by the patentee of disclosure in EP469 that at the very least renders obvious claims 1-18 and 26-32 of the '179 patent. For example, Examples 1-3 of EP469 that correspond to Examples 1-3 of the '179 patent, and Examples 1-3 of EP469 at the very least render obvious that which is claimed in claims 1-18 and 26-32 of the '179 patent. Hence, EP469 (or Exhibit H and Exhibit I.3) at the very least renders claims 1-18 and 26-32 of the '179 patent obvious.

To any extent that the US Patent & Trademark Office considers any of claims 1-18 and 26-32 broader than the disclosure of the applications in the lineage of the '179 patent, whereby none of those applications and Exhibit H provide Section 112, first paragraph, support for such claims, but Exhibit H discloses species of that which is within claims 1-18 and 26-32, the US Patent & Trademark Office may also consider that Exhibit H (or Exhibit H and I.3) anticipates such claims. In this regard, mention is made of *In re Paulsen*, 30 F.3d 1475, 31 USPQ2d 1671(Fed. Cir. 1994) and *In re Baxter Travenol Labs*, 952 F.2d 388, 391, 21 USPQ2d 1281, 1285 (Fed.Cir. 1992) which stand for the proposition that, "anticipation is the ultimate of obviousness." For example, based on the above discussion in Section 3.3, it is respectfully asserted that the recitation of claims 1-8 of "analyzing the amplified DNA sequence to detect the allele", the recitation of claims 26-32 of a "DNA analysis method", and the recitations of "multi-allelic" and "multi-allelic genetic locus" of claims 1-18 and 26-32 broadened these claims beyond the disclosure in the applications in the lineage of the '179 patent such that Exhibit H, disclosing species within claims 1-18 and 26-32 anticipated those claims, as well as rendered them obvious.

Accordingly, Exhibit H (or Exhibit H and I.3) renders obvious or anticipates claims 1-18 and 26-32 of the '179 patent, and presents SNQs that should result in a Reexamination Certificate cancelling claims 1-18 and 26-32 of the '179 patent.

6. CONCLUSION

For the reasons given above, reexamination of claims 1-18 and 26-32 of US Patent 5,612,179 is respectfully requested as there are substantial new questions of patentability in view of the claims being anticipated and/or obvious based on prior art cited herein presented in a new light that convincingly establishes that claim limitations of the '179 patent were not correctly considered in the previous examination and reexamination proceedings. Moreover, for the reasons given herein, not only should this Request for Reexamination be granted, but a Reexamination Certificate should issue cancelling all of claims 1-18 and 26-32 of US Patent 5,612,179; and such relief is respectfully requested.

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Respectfully submitted,
MERIAL LTD, and
VEDDER PRICE P.C., Counsel for Merial Ltd.

Judy Jarecki-Black, by Thomas J. Kowalski, Reg. No. 32,147

By: Judy Jarecki-Black, by Thomas J. Kowalski, Reg. No. 32,147

Judy C. Jarecki-Black, PhD, Esq
Reg. No. 44,170
Tel. No. (678) 638-3805
Fax No. (678) 638-3350
Chad M. Kitchen, PhD, PA
Reg. No. 65,922
Tel. No. (678) 638-3473
Thomas J. Kowalski, Esq
Reg. No. 32,147
Tel. No. (212) 407-7640
Smitha B.Uthaman, PhD, PA
Reg. No. L0613
Tel. No. (212) 407-7646