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(54) Titre : PROCEDE DE SELECTION D'INDICATIONS THERAPEUTIQUES
(54) Title: METHOD OF SELECTING THERAPEUTIC INDICATIONS

(57) **Abrégé/Abstract:**

Methods are provided for repositioning a pharmaceutical, comprising the steps of: a. selecting at least one target gene or gene product associated with the treatment of at least one first disease, trait and/or phenotype by said pharmaceutical, b. identifying at least one second disease, trait and/or phenotype for at least one target gene of pharmaceutical mentioned in (a) using genome-wide associated studies, and c. selecting at least one second disease, trait and/or phenotype based on step (b) for treatment with said pharmaceutical compound in step (a). Methods are provided for treating Crohn's disease in a human in need thereof, comprising administering denosumab to said human.



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(54) Title: METHOD OF SELECTING THERAPEUTIC INDICATIONS

(57) **Abstract:** Methods are provided for repositioning a pharmaceutical, comprising the steps of: a. selecting at least one target gene or gene product associated with the treatment of at least one first disease, trait and/or phenotype by said pharmaceutical, b. identifying at least one second disease, trait and/or phenotype for at least one target gene of pharmaceutical mentioned in (a) using genome-wide associated studies, and c. selecting at least one second disease, trait and/or phenotype based on step (b) for treatment with said pharmaceutical compound in step (a). Methods are provided for treating Crohn's disease in a human in need thereof, comprising administering denosumab to said human.



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METHOD OF SELECTING THERAPEUTIC INDICATIONS

Field of the Invention

The invention relates to methods for selecting a therapeutic indication for a pharmaceutical as well as methods of treating various disease and disorders with a pharmaceutical.

Background of the Invention

A genome-wide association study (GWAS) is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. In theory, once new genetic associations are identified, researchers can use the information to develop medicines to treat and prevent the disease. However, the promise that genome-wide associated studies (GWAS) studies will lead to novel therapeutics has not yet materialized partly because of the 10+ year lag time between identifying a new drug target discovering and developing novel medicines to the target.

Thus, methods are needed for translating GWAS results to identify new or unsuspected indications for existing pharmaceuticals. Additionally, methods are needed for validating or invalidating a first therapeutic indication of a pharmaceutical as well as selecting at least a therapeutic agent for treatment or prevention of a disease and/or disorder.

Brief Description of the Drawings

Figure 1: Analysis pipeline: 991 GWAS associated genes were selected from the GWAS catalog after two filtering steps (see material and methods for details). These genes were evaluated as potential drug targets for small molecules and bipharmaceuticals. 155 of these 991 genes were also targeted by drugs currently in pharmaceutical pipelines based on the Pharmaprojects database that has 1,089 genes targeted by drugs. When the disease for the drug was identical to the GWAS disease trait for the gene it increased the confidence that the drug was for an appropriate disease indication. When it was different it could be a potential opportunity to use the drug for the disease trait the GWAS. 63 individual genes

map to 52 different GWAS traits and drugs with the same or closely related indication to the GWAS traits (considered as matches). 92 individual genes map to 51 GWAS traits and drugs with indications different from the GWAS traits (considered mismatches or potential drug repositioning opportunities). Some genes are in both lists as they have multiple GWAS phenotypes that resulted in both a match to an indication and also a novel indication.

Summary of the Invention

Methods are provided for treating Crohn's disease in a human in need thereof, comprising administering denosumab to said human.

Methods are provided for treating Crohn's disease in a human in need thereof, comprising administering to said human at least one compound selected from the group consisting of: an inhibitor and/or antagonist of tumor necrosis factor ligand, a T-cell co-stimulatory ligand, an IL-18 receptor antagonist and/or inhibitor, inducer of IL27 expression, anti-IL2 receptor mAb, chemokine (C-C motif) ligand 2 inhibitor and/or antagonist, estrogen related receptor alpha binding agent, galactosylceramidase, anti-Intercellular adhesion molecule 3 (ICAM3) mAb, anti-ICOS mAb, IL-23 receptor inhibitor and/or antagonist, Janus kinase 2 inhibitor, leucine-rich repeat kinase 2 inhibitor, mucin 1, cell surface associated inhibitor, signal transducer and activator of transcription 3 (acute-phase response factor) inhibitor, and tyrosine kinase 2 inhibitor.

Methods are provided for treating multiple sclerosis in a human in need thereof, comprising administering a STAT3 inhibitor to said human.

Methods are provided for repositioning a pharmaceutical, comprising the steps of:

- a. selecting at least one target gene or gene product associated with the treatment of at least one first disease, trait and/or phenotype by said pharmaceutical,
- b. identifying at least one second disease, trait and/or phenotype for at least one target gene of pharmaceutical mentioned in (a) using genome-wide associated studies, and
- c. selecting at least one second disease, trait and/or phenotype based on step (b) for treatment with said pharmaceutical compound in step (a).

Methods are also provided for validating or invalidating a first therapeutic indication of a pharmaceutical comprising matching all GWAS associated diseases, traits and/or phenotypes of at least one target gene associated with said first therapeutic indication and determining if at least one GWAS associated disease, trait and/or phenotype of said target gene is associated with said first therapeutic indication.

Methods are also provided for selecting a therapeutic agent for treatment or prevention of a disease comprising the steps of:

- a. selecting at least one target gene or gene product associated with at least one disease, trait and/or phenotype by at least one genome-wide associated study;
- b. optionally determining if said target gene or gene product is small molecule druggable, secreted protein, antibody accessible, or modifiable by some other modality including anti-sense oligos, gene therapy, aptamers;
- c. determining if said target is under expressed or over expressed for a particular disease, trait and/or phenotype;
- d. selecting a therapeutic agent that is an agonist to said target gene or gene product if said gene is under reduced functionality in said disease and/or trait of step (a) and selecting a therapeutic agent that is an antagonist to said target gene or gene product if said gene is under increased functionality in a particular disease and/or trait.

Detailed Description

With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers now have a set of research tools that make it possible to find the genetic contributions to common diseases. The tools include computerized databases that contain the reference human genome sequence, a map of human genetic variation and a set of new technologies that can quickly and accurately analyze whole-genome samples for genetic variations that contribute to the onset of a disease.

To carry out a genome-wide association study, researchers obtain DNA from participants in one of two groups: people with a selected disease, trait and/or phenotype and similar people without that disease trait and/or phenotype. Each person's complete set of DNA, or genome, is surveyed for strategically selected markers of genetic variation, which are called single nucleotide polymorphisms, or SNPs. If certain genetic variations are found to be significantly more frequent in people with the disease compared to people

without disease, the variations are said to be "associated" with the disease. The associated genetic variations can serve as powerful pointers to the region of the human genome where the disease-causing problem resides.

Associated variants may either directly or indirectly cause selected disease, trait
5 and/or phenotype. Therefore, further genotyping of DNA base pairs in a particular region of the genome may be necessary to identify the exact genetic change involved in the selected disease, trait and/or phenotype.

As used herein, "genotyping" a subject (or DNA or other biological sample) for a polymorphic allele of a gene(s) means detecting which allelic or polymorphic form(s) of
10 the gene(s) or gene expression products (*e.g.*, hnRNA, mRNA or protein) are present or absent in a subject (or a sample). Related RNA or protein expressed from such gene may also be used to detect polymorphic variation. As is well known in the art, an individual may be heterozygous or homozygous for a particular allele. More than two allelic forms may exist, thus, there may be more than three possible genotypes. For purposes of the
15 present invention, "genotyping" includes the determination of HLA alleles using suitable serologic techniques, as are known in the art. As used herein, an allele may be 'detected' when other possible allelic variants have been ruled out; *e.g.*, where a specified nucleic acid position is found to be neither adenine (A), thymine (T) or cytosine (C), it can be concluded that guanine (G) is present at that position (*i.e.*, G is 'detected' or 'diagnosed' in
20 a subject). Sequence variations may be detected directly (by, *e.g.*, sequencing) or indirectly (*e.g.*, by restriction fragment length polymorphism analysis, or detection of the hybridization of a probe of known sequence, or reference strand conformation polymorphism), or by using other known methods.

As used herein, a "genetic subset" of a population consists of those members of the
25 population having a particular genotype. In the case of a biallelic polymorphism, a population can potentially be divided into three subsets: homozygous for allele 1 (1,1), heterozygous (1,2), and homozygous for allele 2 (2,2). A 'population' of subjects may be defined using various criteria, *e.g.*, individuals being treated with lapatinib or individuals with cancer.

30 As used herein, a subject that is "predisposed to" or "at increased risk of" a particular disease, trait and/or phenotypic response based on genotyping will be more likely to display that phenotype than an individual with a different genotype at the target

polymorphic locus (or loci). Where the phenotypic response is based on a multi-allelic polymorphism, or on the genotyping of more than one gene, the relative risk may differ among the multiple possible genotypes.

5 An allele refers to one specific form of a genetic sequence (such as a gene) within a cell, a sample, an individual or within a population, the specific form differing from other forms of the same gene in the sequence of at least one, and frequently more than one, variant sites within the sequence of the gene. The sequences at these variant sites that differ between different alleles are termed "variants", "polymorphisms", or "mutations." In general, polymorphism is used to refer to variants that have a frequency of at least 1% in a population, while the term mutation is generally used for variants that occur at a frequency
10 of less than 1% in a population. In diploid organisms such as humans, at each autosomal specific chromosomal location or "locus" an individual possesses two alleles, a first inherited from one parent and a second inherited from the other parent, for example one from the mother and one from the father. An individual is "heterozygous" at a locus if it
15 has two different alleles at the locus. An individual is "homozygous" at a locus if it has two identical alleles at that locus.

A polymorphism may comprise one or more base changes, an insertion, a repeat, or a deletion. A polymorphic locus may be as small as one base pair. Polymorphic markers include restriction fragment length polymorphisms, variable number of tandem repeats
20 (VNTR's), hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats, simple sequence repeats, and insertion elements such as Alu. The first identified allelic form is arbitrarily designated as the reference form and other allelic forms are designated as alternative or variant alleles. The allelic form occurring most frequently in a selected population is sometimes referred to as the wild type form. The
25 most frequent allele may also be referred to as the major allele and the less frequent allele as the minor allele. Diploid organisms may be homozygous or heterozygous for allelic forms. A diallelic polymorphism has two forms. A triallelic polymorphism has three forms. A polymorphism between two nucleic acids can occur naturally, or be caused by exposure to or contact with chemicals, enzymes, or other agents, or exposure to agents that
30 cause damage to nucleic acids, for example, ultraviolet radiation, mutagens or carcinogens.

Single nucleotide polymorphisms (SNPs) are positions at which two alternative bases occur at appreciable frequency (>1%) in the human population, and are the most

common type of human genetic variation. Approximately 90% of all polymorphisms in the human genome are SNPs. SNPs are single base positions in DNA at which different alleles, or alternative nucleotides, exist in a population. An individual may be homozygous or heterozygous for an allele at each SNP position. A SNP can, in some instances, be referred to as a "cSNP" to denote that the nucleotide sequence containing the SNP is an amino acid coding sequence. As used herein, references to SNPs and SNP genotypes include individual SNPs and/or haplotypes, which are groups of SNPs that are generally inherited together. Haplotypes can have stronger correlations with diseases or other phenotypic effects compared with individual SNPs, and therefore may provide increased diagnostic accuracy in some cases (Stephens *et al. Science* 293, 489-493, 20 Jul. 2001).

Causative SNPs are those SNPs that produce alterations in gene expression or in the expression, structure, and/or function of a gene product, and therefore are most predictive of a possible clinical phenotype. One such class includes SNPs falling within regions of genes encoding a polypeptide product, i.e. cSNPs. These SNPs may result in an alteration of the amino acid sequence of the polypeptide product (i.e., non-synonymous codon changes) and give rise to the expression of a defective or other variant protein. Furthermore, in the case of nonsense mutations, a SNP may lead to premature termination of a polypeptide product. Causative SNPs do not necessarily have to occur in coding regions; causative SNPs can occur in, for example, any genetic region that can ultimately affect the expression, structure, and/or activity of the protein encoded by a nucleic acid. Such genetic regions include, for example, those involved in transcription, such as SNPs in transcription factor binding domains, SNPs in promoter regions, in areas involved in transcript processing, such as SNPs at intron-exon boundaries that may cause defective splicing, or SNPs in mRNA processing signal sequences such as polyadenylation signal regions. Some SNPs that are not causative SNPs nevertheless are in close association with, and therefore segregate with, a disease-causing sequence. In this situation, the presence of a SNP correlates with the presence of, or predisposition to, or an increased risk in developing the disease. These SNPs, although not causative, are nonetheless also useful for diagnostics, disease predisposition screening, and other uses.

An association study of a SNP and a specific disorder or a predisposition to a safety event involves determining the presence or frequency of the SNP allele in biological

samples from individuals with the disorder or predisposition to a safety event of interest and comparing the information to that of controls (i.e., individuals who do not have the disorder or experience the same safety event).

5 A SNP may be screened in diseased tissue samples or any biological sample obtained from an individual, and compared to control samples, and selected for its increased (or decreased) occurrence in a specific pathological condition. Once a statistically significant association is established between one or more SNP(s) and a pathological condition (or other phenotype) of interest, then the region around the SNP can optionally be thoroughly screened to identify the causative genetic locus/sequence(s) (e.g.,
10 causative SNP/mutation, gene, regulatory region, etc.) that influences the pathological condition or phenotype.

Clinical trials have shown that patient response to treatment with pharmaceuticals is often heterogeneous. There is a continuing need to improve pharmaceutical agent design and therapy. In that regard, SNPs can be used to identify patients most suited to
15 therapy with particular pharmaceutical agents (this is often termed "pharmacogenomics"). Similarly, SNPs can be used to exclude patients from certain treatment due to the patient's increased likelihood of developing toxic side effects or their likelihood of not responding to the treatment. Pharmacogenomics can also be used in pharmaceutical research to assist the drug development and selection process. (Linder et al. (1997), Clinical Chemistry, 43,
20 254; Marshall (1997), Nature Biotechnology, 15, 1249; International Patent Application WO 97/40462, Spectra Biomedical; and Schafer et al. (1998), Nature Biotechnology, 16, 3).

Several techniques for the detection of mutations have evolved based on the principal of hybridization analysis. For example, in the primer extension assay, the DNA
25 region spanning the nucleotide of interest is amplified by PCR, or any other suitable amplification technique. After amplification, a primer is hybridized to a target nucleic acid sequence, wherein the last nucleotide of the 3' end of the primer anneals immediately 5' to the nucleotide position on the target sequence that is to be analyzed. The annealed primer is extended by a single, labelled nucleotide triphosphate. The incorporated nucleotide is
30 then detected.

The sequence of any nucleic acid including a gene or PCR product or a fragment or portion thereof may be sequenced by any method known in the art (e.g., chemical

sequencing or enzymatic sequencing). "Chemical sequencing" of DNA may denote methods such as that of Maxam and Gilbert (1977) (Proc. Natl. Acad. Sci. USA 74:560), in which DNA is randomly cleaved using individual base-specific reactions. "Enzymatic sequencing" of DNA may denote methods such as that of Sanger (Sanger, et al., (1977) Proc. Natl. Acad. Sci. USA 74:5463).

Conventional molecular biology, microbiology, and recombinant DNA techniques including sequencing techniques are well known among those skilled in the art. Such techniques are explained fully in the literature. See, e.g., Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual*, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (herein "Sambrook, et al., 1989"); DNA Cloning: A Practical Approach, Volumes I and II (D. N. Glover ed. 1985); *Oligonucleotide Synthesis* (M. J. Gait ed. 1984); *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. (1985)); *Transcription And Translation* (B. D. Hames & S. J. Higgins, eds. (1984)); *Animal Cell Culture* (R. I. Freshney, ed. (1986)); *Immobilized Cells And Enzymes* (IRL Press, (1986)); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); F. M. Ausubel, et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994

The Peptide Nucleic Acid (PNA) affinity assay is a derivative of traditional hybridization assays (Nielsen et al., *Science* 254:1497-1500 (1991); Egholm et al., *J. Am. Chem. Soc.* 114:1895-1897 (1992); James et al., *Protein Science* 3:1347-1350 (1994)). PNAs are structural DNA mimics that follow Watson-Crick base pairing rules, and are used in standard DNA hybridization assays. PNAs display greater specificity in hybridization assays because a PNA/DNA mismatch is more destabilizing than a DNA/DNA mismatch and complementary PNA/DNA strands form stronger bonds than complementary DNA/DNA strands.

DNA microarrays have been developed to detect genetic variations and polymorphisms (Taton *et al.*, *Science* 289:1757-60, 2000; Lockhart et al., *Nature* 405:827-836 (2000); Gerhold *et al.*, *Trends in Biochemical Sciences* 24:168-73 (1999); Wallace, R. W., *Molecular Medicine Today* 3:384-89 (1997); Blanchard and Hood, *Nature Biotechnology* 149:1649 (1996)). DNA microarrays are fabricated by high-speed robotics, on glass or nylon substrates, and contain DNA fragments with known identities ("the probe"). The microarrays are used for matching known and unknown DNA fragments ("the target") based on traditional base-pairing rules.

The Protein Truncation Test (PTT) is also commonly used to detect genetic polymorphisms (Roest *et al.*, *Human Molecular Genetics* 2:1719-1721, (1993); Van Der Luit *et al.*, *Genomics* 20:1-4 (1994); Hogervorst *et al.*, *Nature Genetics* 10: 208-212 (1995)). Typically, in the PTT, the gene of interest is PCR amplified, subjected to *in vitro* transcription/translation, purified, and analyzed by polyacrylamide gel electrophoresis.

“Genetic testing” (also called genetic screening) as used herein refers to the testing of a biological sample from a subject to determine the subject’s genotype; and may be utilized to determine if the subject’s genotype comprises alleles that either cause, or increase susceptibility to, a particular phenotype (or that are in linkage disequilibrium with allele(s) causing or increasing susceptibility to that phenotype).

“Linkage disequilibrium” refers to the tendency of specific alleles at different genomic locations to occur together more frequently than would be expected by chance. Alleles at given loci are in complete equilibrium if the frequency of any particular set of alleles (or haplotype) is the product of their individual population frequencies. A commonly used measure of linkage disequilibrium is r :

$$r = \frac{\hat{\Delta}_{AB}}{\sqrt{(\tilde{\pi}_A + \hat{D}_A)(\tilde{\pi}_B + \hat{D}_B)}}$$

where

$$\tilde{\pi}_A = \tilde{p}_A(1-\tilde{p}_A), \tilde{\pi}_B = \tilde{p}_B(1-\tilde{p}_B), \hat{D}_A = \tilde{P}_{AA} - \tilde{p}_A^2, \hat{D}_B = \tilde{P}_{BB} - \tilde{p}_B^2$$

$$\hat{\Delta}_{AB} = \frac{1}{n}n_{AB} - 2\tilde{p}_A\tilde{p}_B$$

nr^2 has an approximate chi square distribution with 1 degree freedom for biallelic markers. Loci exhibiting an r such that nr^2 is greater than 3.84, corresponding to a significant chi-squared statistic at the 0.05 level, are considered to be in linkage disequilibrium (BS Weir 1996 *Genetic Data Analysis II* Sinauer Associates, Sunderland, MD).

Alternatively, a normalized measure of linkage disequilibrium can be defined as:

$$D'_{AB} = \begin{cases} \frac{D_{AB}}{\min(p_A p_B, p_a p_b)}, & D_{AB} < 0 \\ \frac{D_{AB}}{\min(p_A p_b, p_a p_B)}, & D_{AB} > 0 \end{cases}$$

The value of the D' has a range of -1.0 to 1.0. When statistically significant absolute D' value for two markers is not less than 0.3 they are considered to be in linkage

5 disequilibrium.

Polymorphic alleles may be detected by determining the DNA polynucleotide sequence, or by detecting the corresponding sequence in RNA transcripts from the polymorphic gene, or where the nucleic acid polymorphism results in a change in an encoded protein by detecting such amino acid sequence changes in encoded proteins; using
 10 any suitable technique as is known in the art. Polynucleotides utilized for typing are typically genomic DNA, or a polynucleotide fragment derived from a genomic polynucleotide sequence, such as in a library made using genomic material from the individual (e.g. a cDNA library). The polymorphism may be detected in a method that comprises contacting a polynucleotide or protein sample from an individual with a specific
 15 binding agent for the polymorphism and determining whether the agent binds to the polynucleotide or protein, where the binding indicates that the polymorphism is present. The binding agent may also bind to flanking nucleotides and amino acids on one or both sides of the polymorphism, for example at least 2, 5, 10, 15 or more flanking nucleotide or amino acids in total or on each side. In the case where the presence of the polymorphism is
 20 being determined in a polynucleotide it may be detected in the double stranded form, but is typically detected in the single stranded form.

The binding agent may be a polynucleotide (single or double stranded) typically with a length of at least 10 nucleotides, for example at least 15, 20, 30, or more nucleotides. A polynucleotide agent which is used in the method will generally bind to the
 25 polymorphism of interest, and the flanking sequence, in a sequence specific manner (e.g. hybridize in accordance with Watson-Crick base pairing) and thus typically has a sequence which is fully or partially complementary to the sequence of the polymorphism and flanking region. The binding agent may be a molecule that is structurally similar to polynucleotides that comprises units (such as purine or pyrimidine analogs, peptide nucleic
 30 acids, or RNA derivatives such as locked nucleic acids (LNA)) able to participate in

Watson-Crick base pairing. The agent may be a protein, typically with a length of at least 10 amino acids, such as at least 20, 30, 50, or 100 or more amino acids. The agent may be an antibody (including a fragment of such an antibody that is capable of binding the polymorphism).

5 A binding agent can be used as a probe. The probe may be labelled or may be capable of being labelled indirectly. The detection of the label may be used to detect the presence of the probe on (bound to) the polynucleotide or protein of the individual. The binding of the probe to the polynucleotide or protein may be used to immobilize either the probe or the polynucleotide or protein (and, thus, to separate it from one composition or
10 solution).

 Polynucleotides or proteins of the individual can also be immobilized on a solid support and then contacted with the probe. The presence of the probe immobilized to the solid support (via its binding to the polymorphism) is then detected, either directly by detecting a label on the probe or indirectly by contacting the probe with a moiety that
15 binds the probe. In the case of detecting a polynucleotide polymorphism the solid support is generally made of nitrocellulose or nylon. In the case of a protein polymorphism the method may be based on an ELISA system.

 Polymorphism can also be detected using a oligonucleotide ligation assay in which two oligonucleotide probes are used. These probes bind to adjacent areas on the
20 polynucleotide which contains the polymorphism, allowing (after binding) the two probes to be ligated together by an appropriate ligase enzyme. However the two probes will only bind (in a manner which allows ligation) to a polynucleotide that contains the polymorphism, and therefore the detection of the ligated product may be used to determine the presence of the polymorphism.

25 Probes can also be used in a heteroduplex analysis based system to detect polymorphisms. In such a system when the probe is bound to a polynucleotide sequence containing the polymorphism, it forms a heteroduplex at the site where the polymorphism occurs (i.e. it does not form a double strand structure). Such a heteroduplex structure can be detected by the use of an enzyme that is single or double strand specific. Typically the
30 probe is an RNA probe and the enzyme used is RNase H that cleaves the heteroduplex region, thus, allowing the polymorphism to be detected by means of the detection of the cleavage products.

The method may be based on fluorescent chemical cleavage mismatch analysis which is described for example in *PCR Methods and Applications* 3:268-71 (1994) and *Proc. Natl. Acad. Sci.* 85:4397-4401 (1998).

Polymorphisms can also be detected using polynucleotide agents that are able to
5 act as a primer for a PCR reaction only if it binds a polynucleotide containing the
polymorphism (i.e. a sequence- or allele-specific PCR system). Thus, a PCR product will
only be produced if the polymorphism is present in the polynucleotide of the individual,
and the presence of the polymorphism is determined by the detection of the PCR product.
Preferably the region of the primer which is complementary to the polymorphism is at or
10 near the 3' end the primer. The he polynucleotide agent may also bind to the wild-type
sequence but will not act as a primer for a PCR reaction.

The method may be a Restriction Fragment Length Polymorphism (RFLP) based
system. This method can be used if the presence of the polymorphism in the
polynucleotide creates or destroys a restriction site that is recognized by a restriction
15 enzyme. Thus, treatment of a polynucleotide that has such a polymorphism will lead to
different products being produced compared to the corresponding wild-type sequence.
Thus, the detection of the presence of particular restriction digest products can be used to
determine the presence of the polymorphism.

The presence of the polymorphism may be determined based on the change that the
20 presence of the polymorphism makes to the mobility of the polynucleotide or protein
during gel electrophoresis. In the case of a polynucleotide single-stranded conformation
polymorphism (SSCP) analysis may be used. SSCP measures the mobility of the single
stranded polynucleotide on a denaturing gel compared to the corresponding wild-type
polynucleotide, the detection of a difference in mobility indicating the presence of the
25 polymorphism. Denaturing gradient gel electrophoresis (DGGE) is a similar system where
the polynucleotide is electrophoresed through a gel with a denaturing gradient, a difference
in mobility compared to the corresponding wild-type polynucleotide indicating the
presence of the polymorphism.

The presence of the polymorphism may be determined using a fluorescent dye and
30 quenching agent-based PCR assay such as the TAQMAN™ PCR detection system. In
another method of detecting the polymorphism a polynucleotide comprising the

polymorphic region is sequenced across the region which contains the polymorphism to determine the presence of the polymorphism.

Various other detection techniques suitable for use in the present methods will be apparent to those conversant with methods of detecting, identifying, and/or distinguishing polymorphisms. Such detection techniques include but are not limited to direct sequencing, use of “molecular beacons” (oligonucleotide probes that fluoresce upon hybridization, useful in real-time fluorescence PCR; see e.g., Marras et al., Genet Anal 14:151 (1999)); electrochemical detection (reduction or oxidation of DNA bases or sugars; see US Patent No. 5,871,918 to Thorp et al.); rolling circle amplification (see, e.g., Gusev et al., Am J Pathol 159:63 (2001)); Third Wave Technologies (Madison WI) INVADER® non-PCR based detection method (see, e.g., Lieder, Advance for Laboratory Managers, 70 (2000))

Accordingly, any suitable detection technique as is known in the art may be utilized in the present methods.

As used herein, “determining” a subject’s genotype does not require that a genotyping technique be carried out where a subject has previously been genotyped and the results of the previous genetic test are available; determining a subject’s genotype accordingly includes referring to previously completed genetic analyses.

As used herein “pharmaceutical” means any active ingredient capable of treating or preventing at least one disease, trait and/or phenotype. The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington’s Pharmaceutical Sciences (Mack Publishing Company).

As used herein “druggable” means a characteristic that allows a compound or composition to be developed into a drug. For example, a druggable compound or composition could have at least one of the following characteristics: capable of being formulated for administration to a mammal, capable of reaching its target once administered to a mammal, and/or capable of effecting at least one target. Similarly, the term “biopharmable” refers to large molecule such as, but not limited to, proteins, antibodies, antibody fragments, domain antibodies, single chain antibodies, bispecific antibodies, and any combination or variations thereof, aptamers, fusion proteins, synthetic

polypeptides, recombinant polypeptides, vaccines, DNA therapies, and/or RNAi, that can be administered to a mammal.

By the term "treating" and grammatical variations thereof as used herein, is meant therapeutic therapy. In reference to a particular condition, treating means: (1) to
5 ameliorate or prevent the condition of one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition, (3) to alleviate one or more of the symptoms, effects or side effects associated with the condition or treatment thereof, or (4) to slow the progression of the condition or
10 one or more of the biological manifestations of the condition. Prophylactic therapy is also contemplated thereby. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological
15 manifestation thereof. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, such as when a subject has a strong family history of cancer or when a subject has been exposed to a carcinogen.

As used herein "reposition" and "repositioning" and grammatical variations thereof refers to a disease, trait and/or phenotype for which a pharmaceutical may have a use
20 beyond the first disease, trait and/or phenotype for which the pharmaceutical had identified activity.

As used herein the term "amplification" and grammatical variations thereof refers to the presence of one or more extra gene copies in a chromosome complement. In certain embodiments a gene encoding a Ras protein may be amplified in a cell. Amplification of
25 the HER2 gene has been correlated with certain types of cancer. Amplification of the HER2 gene has been found in human salivary gland and gastric tumor-derived cell lines, gastric and colon adenocarcinomas, and mammary gland adenocarcinomas. Semba et al., Proc. Natl. Acad. Sci. USA, 82:6497-6501 (1985); Yokota et al., Oncogene, 2:283-287 (1988); Zhou et al., Cancer Res., 47:6123-6125 (1987); King et al., Science, 229:974-976
30 (1985); Kraus et al., EMBO J., 6:605-610 (1987); van de Vijver et al., Mol. Cell. Biol., 7:2019-2023 (1987); Yamamoto et al., Nature, 319:230-234 (1986).

As used herein “overexpressed” and “overexpression” of a protein or polypeptide and grammatical variations thereof means that a given cell produces an increased number of a certain protein relative to a normal cell of the same type. By way of example, a protein may be overexpressed by diseased cell relative to a normal cell. Additionally, a mutant protein may be overexpressed compared to wild type protein in a cell. As is understood in the art, expression levels of a polypeptide in a cell can be normalized to a housekeeping gene such as actin. In some instances, a certain polypeptide may be underexpressed in a cell compared with a normal or standard cell.

As used herein “at least one target gene” refers to a nucleic acid sequence that encodes any portion of or all of a gene product and/or is operably linked to a nucleic acid encoding a gene product but does not necessarily comprise encoding sequence. By way of example, a nucleic acid sequence necessary for the expression of at least one gene product includes, but is not limited to, enhancers, promoters, regulatory sequences, start codons, stop codons, polyadenylation sequences, and/or encoding sequences. Expression levels of a polypeptide in a particular cell can be effected by, but not limited to, mutations, deletions and/or substitutions of various regulatory elements and/or non-encoding sequence in the cell genome. A gene may have one or more allelic variants, splice variants, derivative variants, substitution variants, deletion variants, truncation variants, and/or insertion variants, fusion polypeptides, orthologs, and/or interspecies homologs.

As used herein “gene product” refers to any portion or all of a protein or polypeptide encoded by at least one target gene. A gene product may be wild type or mutated. Gene products also include any polypeptide having or encoded by a target gene having one or more allelic variants, splice variants, derivative variants, substitution variants, deletion variants, truncation variants, and/or insertion variants, fusion polypeptides, orthologs, and/or interspecies homologs. By way of example, a gene product would include a protein in which part of all of the sequence of a polypeptide or gene encoding the protein is absent or not expressed in the cell. A gene product may be produced by a cell in a truncated form and the sequence of the truncated form may be wild type over the sequence of the truncate. A deletion may mean the absence of all or part of a gene or protein encoded by a gene. Additionally, some of a protein expressed in or encoded by a cell may be mutated while other copies of the same protein produced in the same cell may be wild type. By way of another example a mutation in a protein would

include a protein having one or more amino acid differences in its amino acid sequence compared with wild type of the same protein.

As used herein "loci" refers to a specific location of a gene and/or a DNA sequence on a chromosome.

5

In one embodiment of the present invention, methods are provided for treating Crohn's disease in a human in need thereof, comprising administering denosumab to said human. In one aspect, the present invention embodies the use of denosumab for the treatment of Crohn's disease. In one aspect, the present invention embodies the use of
10 denosumab in the manufacture of a medicament for the treatment of Crohn's disease.

Crohn's disease is a form of inflammatory bowel disease (IBD). It usually affects the intestines, but may occur anywhere from the mouth to the end of the rectum (anus).

Denosumab which is sold under the tradename Prolia® is a human monoclonal antibody for the treatment of osteoporosis, treatment-induced bone loss, bone metastases,
15 rheumatoid arthritis, multiple myeloma, and giant cell tumor of bone. It was developed by the biotechnology company Amgen. Denosumab is designed to target RANKL (RANK ligand), a protein that acts as the primary signal for bone removal. In many bone loss conditions, RANKL overwhelms the body's natural defenses against bone destruction. Antibodies to RANKL are described, for instance, in US Patent No. 6,740,522 and US
20 Patent No. 7,411,050. Denosumab is administered as a 60 mg (1mL) injection every six months for osteoporosis treatment.

In one embodiment of the present invention, methods are provided for treating Crohn's disease in a human in need thereof, comprising administering to said human at least one compound selected from the group consisting of: an inhibitor and/or antagonist
25 of tumor necrosis factor ligand, a T-cell co-stimulatory ligand, an IL-18 receptor antagonist and/or inhibitor, inducer of IL27 expression, anti-IL2 receptor mAb, chemokine (C-C motif) ligand 2 inhibitor and/or antagonist, estrogen related receptor alpha binding agent, galactosylceramidase, anti-Intercellular adhesion molecule 3 (ICAM3) mAb, anti-ICOS mAb, IL-23 receptor inhibitor and/or antagonist, Janus kinase 2 inhibitor, leucine-rich repeat kinase 2 inhibitor, mucin 1, cell surface associated inhibitor, signal transducer
30 and activator of transcription 3 (acute-phase response factor) inhibitor, and tyrosine kinase 2 inhibitor.

In one embodiment, the human also has Celiac disease, irritable bowel syndrome and or inflammatory bowel disease.

In one embodiment, the compound is a tumor necrosis factor ligand antagonist.

In one embodiment, the tumor necrosis factor ligand is member 11 or receptor
5 activator of nuclear factor kappa-B ligand (RANKL). In one embodiment, the tumor necrosis factor ligand is member 15.

In one embodiment, the antagonist is a monoclonal antibody. In one embodiment, the monoclonal antibody is humanized. In one embodiment, the monoclonal antibody is a human antibody. In one embodiment, the monoclonal antibody is denosumab or a
10 functional fragment thereof.

An "antibody" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies,
15 but also fragments thereof (such as Fab, Fab', F(ab').sub.2, Fv), single chain (ScFv), mutants thereof, naturally occurring variants, fusion proteins comprising an antibody portion with an antigen recognition site of the required specificity, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity.

20 A "monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an antigen. Monoclonal antibodies are highly specific, being directed against a single antigenic site. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length
25 monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab').sub.2, Fv), single chain (ScFv), mutants thereof, fusion proteins comprising an antibody portion, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity and the ability to bind to an antigen. It is not
30 intended to be limited as regards to the source of the antibody or the manner in which it is made (e.g., by hybridoma, phage selection, recombinant expression, transgenic animals,

etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

"Altered antibody" refers to a protein encoded by an altered immunoglobulin coding region, which may be obtained by expression in a selected host cell. Such altered
5 antibodies include engineered antibodies (e.g., chimeric, reshaped, humanized or vectored antibodies) or antibody fragments lacking all or part of an immunoglobulin constant region, e.g., Fv, Fab, or F(ab)₂ and the like.

A "chimeric antibody" refers to a type of engineered antibody which contains a naturally-occurring variable region (light chain and heavy chains) derived from a donor
10 antibody in association with light and heavy chain constant regions derived from an acceptor antibody.

A "humanized antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In
15 addition, framework support residues may be altered to preserve binding affinity (see, e.g., Queen et al., Proc. Natl Acad Sci USA, 86:10029-10032 (1989), Hodgson et al., Bio/Technology, 9:421 (1991)). A suitable human acceptor antibody may be one selected from a conventional database, e.g., the KABAT® database, Los Alamos database, and Swiss Protein database, by homology to the nucleotide and amino acid sequences of the
20 donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be noted that the
25 acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody. The prior art describes several ways of producing such humanised antibodies – see for example EP-A-0239400 and EP-A-054951.

The term "donor antibody" refers to an antibody (monoclonal, and/or recombinant) which contributes the amino acid sequences of its variable regions, CDRs, or other
30 functional fragments or analogs thereof to a first immunoglobulin partner, so as to provide the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

The term "acceptor antibody" refers to an antibody (monoclonal and/or recombinant) heterologous to the donor antibody, which contributes all (or any portion, but preferably all) of the amino acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. Preferably a human antibody is the acceptor antibody.

"CDRs" are defined as the complementarity determining region amino acid sequences of an antibody which are the hypervariable regions of immunoglobulin heavy and light chains. See, e.g., Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987). There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, or all three light chain CDRs (or both all heavy and all light chain CDRs, if appropriate). The structure and protein folding of the antibody may mean that other residues are considered part of the antigen binding region and would be understood to be so by a skilled person. See for example Chothia et al., (1989) Conformations of immunoglobulin hypervariable regions; Nature 342, p877-883.

CDRs provide the majority of contact residues for the binding of the antibody to the antigen or epitope. CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, and include analogs of the naturally occurring CDRs, which analogs also share or retain the same antigen binding specificity and/or neutralizing ability as the donor antibody from which they were derived.

A "functional fragment" is a partial heavy or light chain variable sequence (e.g., minor deletions at the amino or carboxy terminus of the immunoglobulin variable region) which retains the same antigen binding specificity and the same or similar neutralizing ability as the antibody from which the fragment was derived.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the

germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

In one embodiment of the present invention methods are provided for treating Crohn's disease in a human in need thereof, comprising administering a T-cell co-stimulator to said human. The T-cell co-stimulator may be an antibody that binds B7 related proteins. In one aspect the antibody is a human antibody that binds to B7 related protein-1 (B7RP-1).

In one embodiment of the present invention, methods are provided for treating Crohn's disease in a human in need thereof, comprising administering an inhibitor of signal transducer and activator of transcription 3 (STAT3) to said human.

The STAT3 inhibitors can be selected from one or more of the following: OPB-31121; OPB-51602; Bardoxolone methyl; Brivudine, and RESprote.

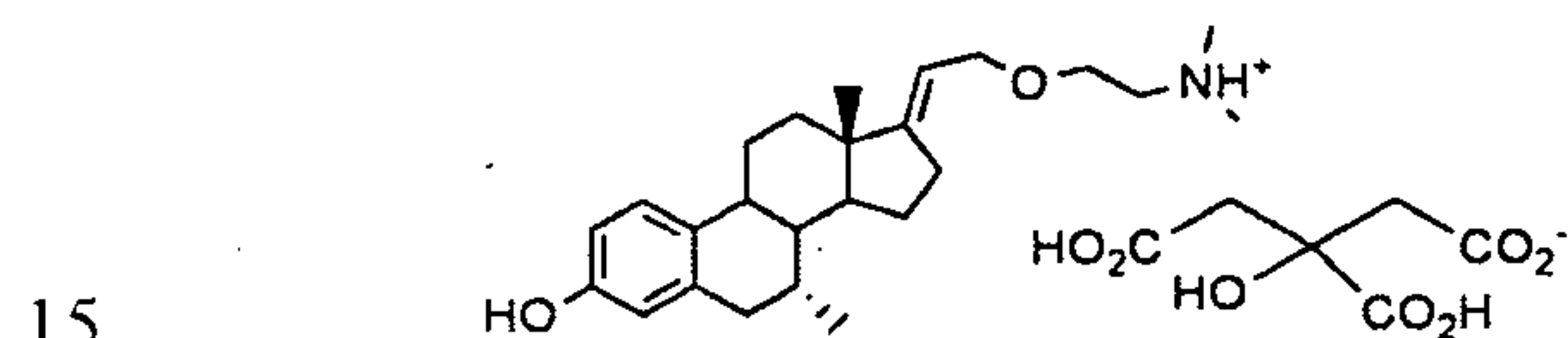
TNF inhibitors include, but are not limited to, monoclonal antibodies such as infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi), or with a circulating receptor fusion protein such as etanercept (Enbrel). Other TNF inhibitors include xanthine derivatives (e.g. pentoxifylline) and Bupropion.

IL-18 receptor proteins as well as proteins that bind to them, including antibodies, are described in US Patent Nos. 7,704,945, 7,141,393; 7,169,581; and 8,105,805. Polypeptides, including antibodies, that bind to IL-18 are described in US Patent Nos. 6,559,298; 6,589,764; and 7,767,207.

Examples of an anti-IL2 receptor mAb, include, but are not limited to, inolimomab, basiliximab, and daclizumab. Inolimomab is a mouse monoclonal antibody developed as an immunosuppressive drug against graft-versus-host disease. Its target is the alpha chain of the interleukin-2 receptor. Basiliximab (trade name Simulect) is a chimeric mouse-human monoclonal antibody to the α chain (CD25) of the IL-2 receptor of T cells. It is used to prevent rejection in organ transplantation, especially in kidney transplants. Daclizumab (trade name Zenapax) is a therapeutic humanized monoclonal antibody to the alpha subunit of the IL-2 receptor of T cells. It is used to prevent rejection in organ transplantation, especially in kidney transplants.

Chemokine (C-C motif) ligand 2 (CCL2) also known as monocyte chemotactic protein-1 (MCP-1) or small inducible cytokine A2 is a protein that in humans is encoded by the CCL2 gene. CCL2 is a small cytokine belonging to the CC chemokine family. CCL2 recruits monocytes, memory T cells, and dendritic cells to sites of tissue injury, infection, and inflammation. CCL2 plays a significant role in the CCL2/CCR2 pathway in lipoatrophy-induced diabetes. (Yang, et al. Diabetologia. 2009 May; 52(5):972-81).

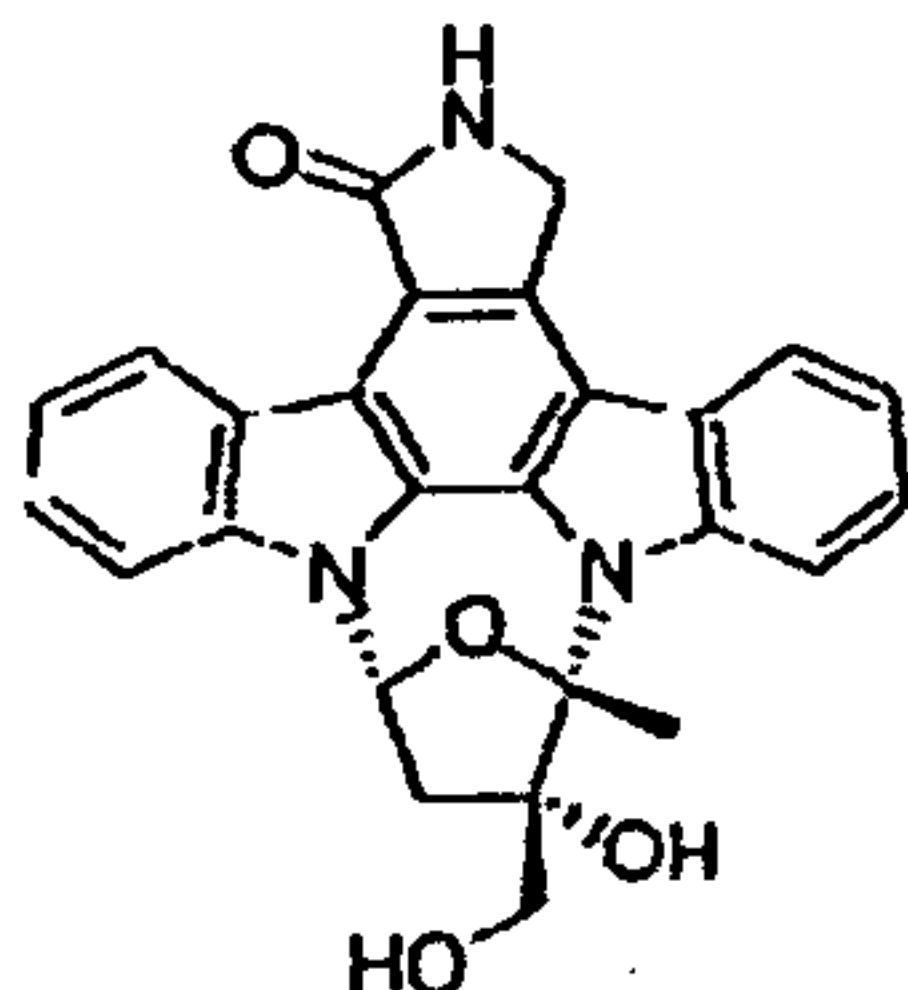
The orphan nuclear receptor estrogen-related receptor alpha (ERRalpha) has been implicated in the development of various human malignancies, including breast, prostate, ovary, and colon cancer. SR16388 (21-[2-(N,N-Dimethylamino)ethyl]oxy-7a-methyl-19-norpregna-1,3,5(10),17(20)-tetraen-3-ol citrate salt) is an orally active compound that belongs to the antiestrogen class of therapeutic agents. SR16388 is a potent and selective inhibitor of human ERR α , which does not bind estrogen (E2). SR16388 is represented by the following formula (Duellman, et al Biochem Pharmacol. 2010 September 15; 80(6): 819-826).



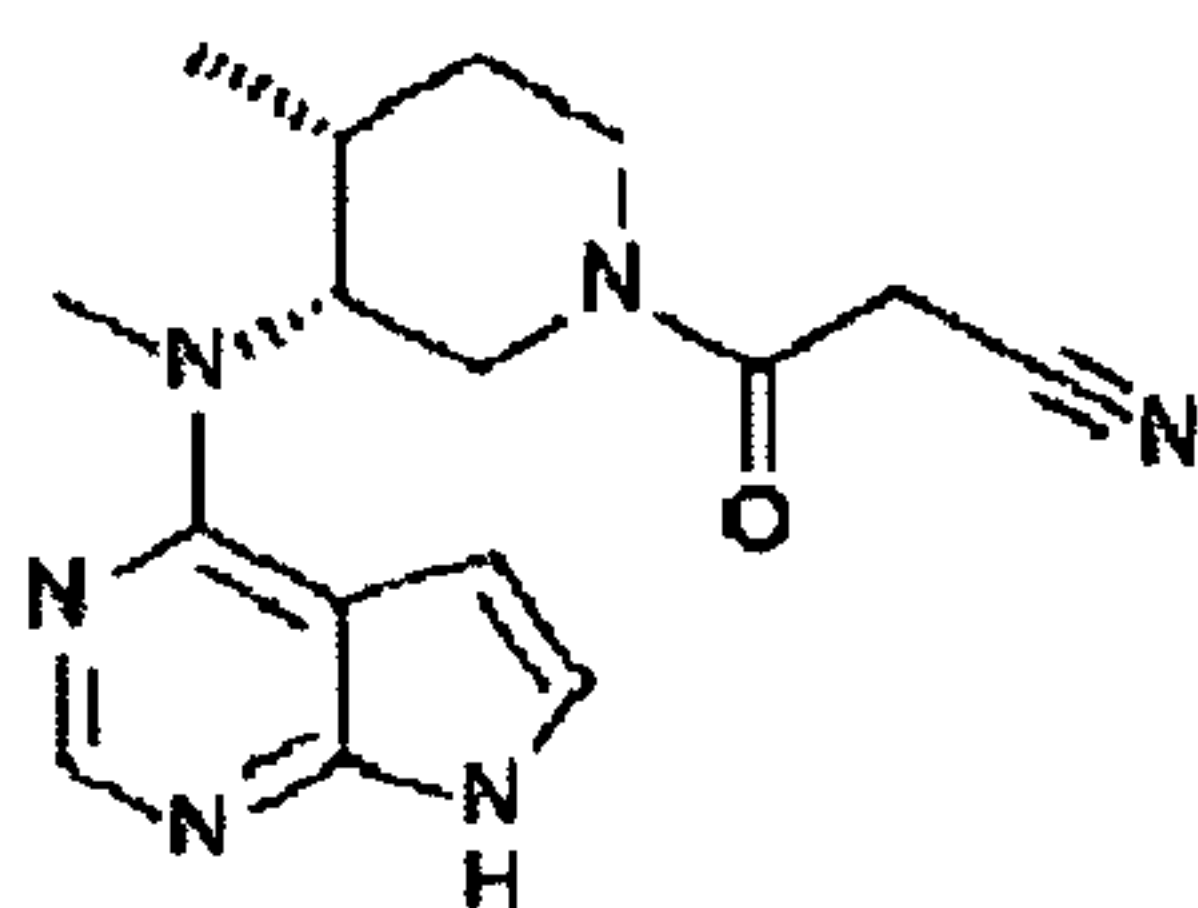
Galactosylceramidase (or galactocerebrosidase) is an enzyme that in humans is encoded by the *GALC* gene. Galactosylceramidase is an enzyme which removes galactose from ceramide derivatives (galactocerebrosides). Galactosylceramidase is a lysosomal protein which hydrolyzes the galactose ester bonds of galactocerebroside, galactosylsphingosine, lactosylceramide, and monogalactosyldiglyceride.

Janus kinase inhibitor is a class of medicines that function by inhibiting the effect of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2), interfering with the JAK-STAT signaling pathway. Some JAK2 inhibitors are under development for the treatment of polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Some inhibitors of JAK2 are in clinical trials, e.g. for psoriasis. JAK3 is also being targeted for a variety of inflammatory diseases, and one has had good results in a phase II trial for rheumatoid arthritis. Janus kinase inhibitors include but are not limited to:

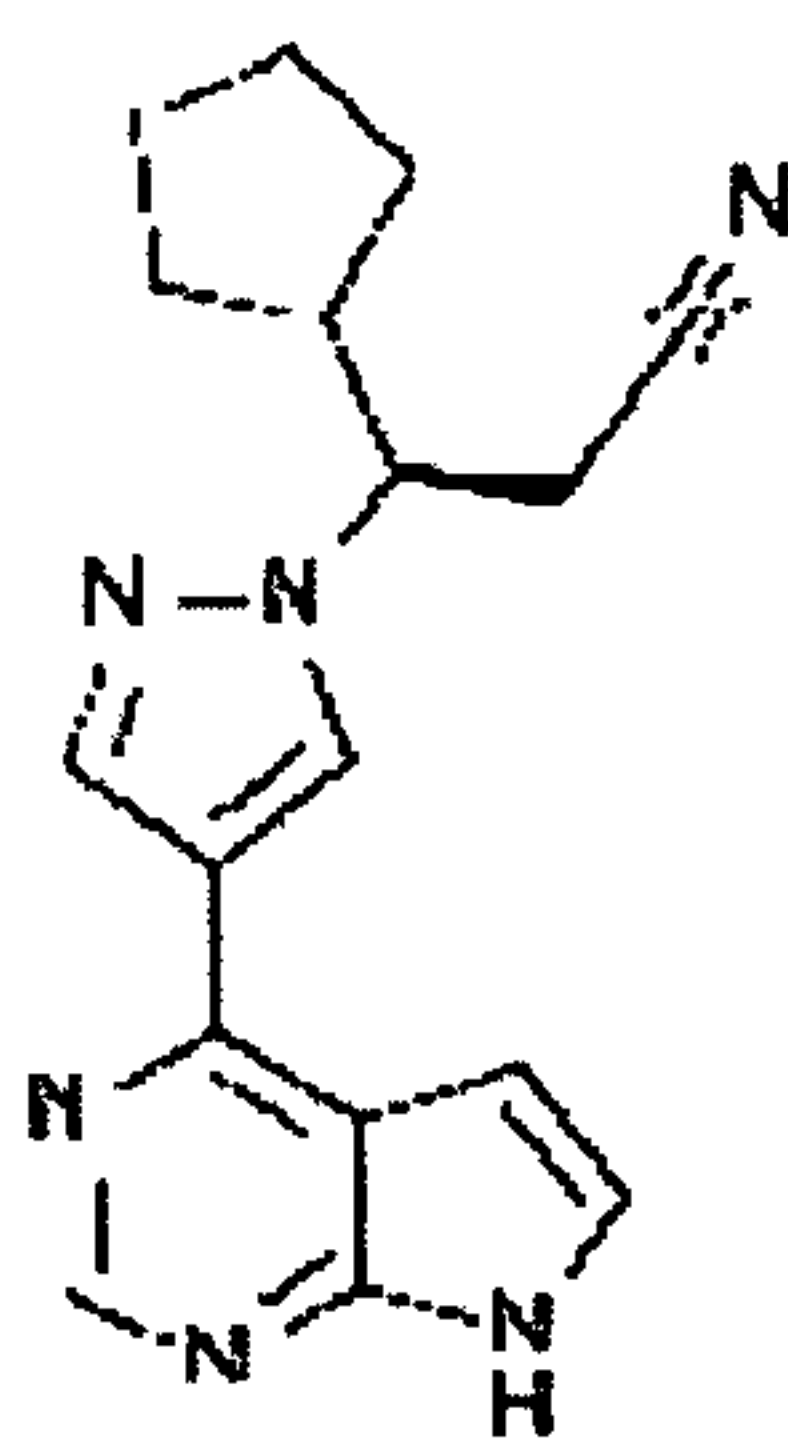
Lestaurtinib against JAK2, for acute myelogenous leukemia (AML) which is represented by the formula:



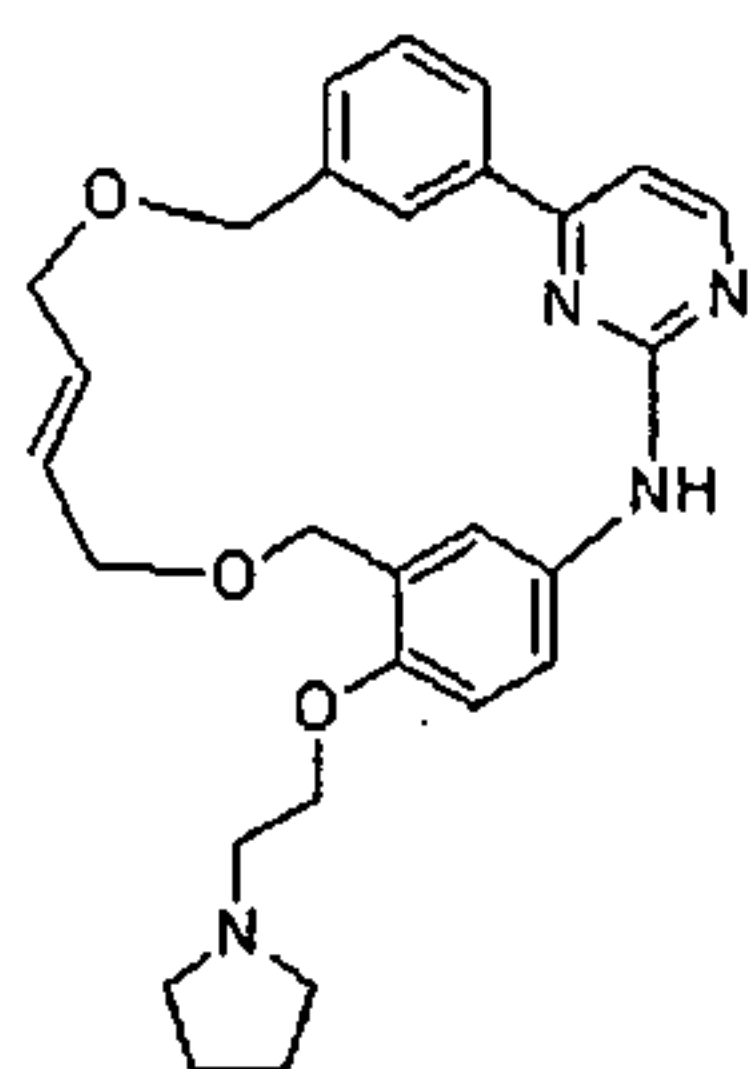
Tofacitinib (previously called tasocitinib) (CP-690550) against JAK3 for psoriasis,
5 and rheumatoid arthritis shown in the following formula:



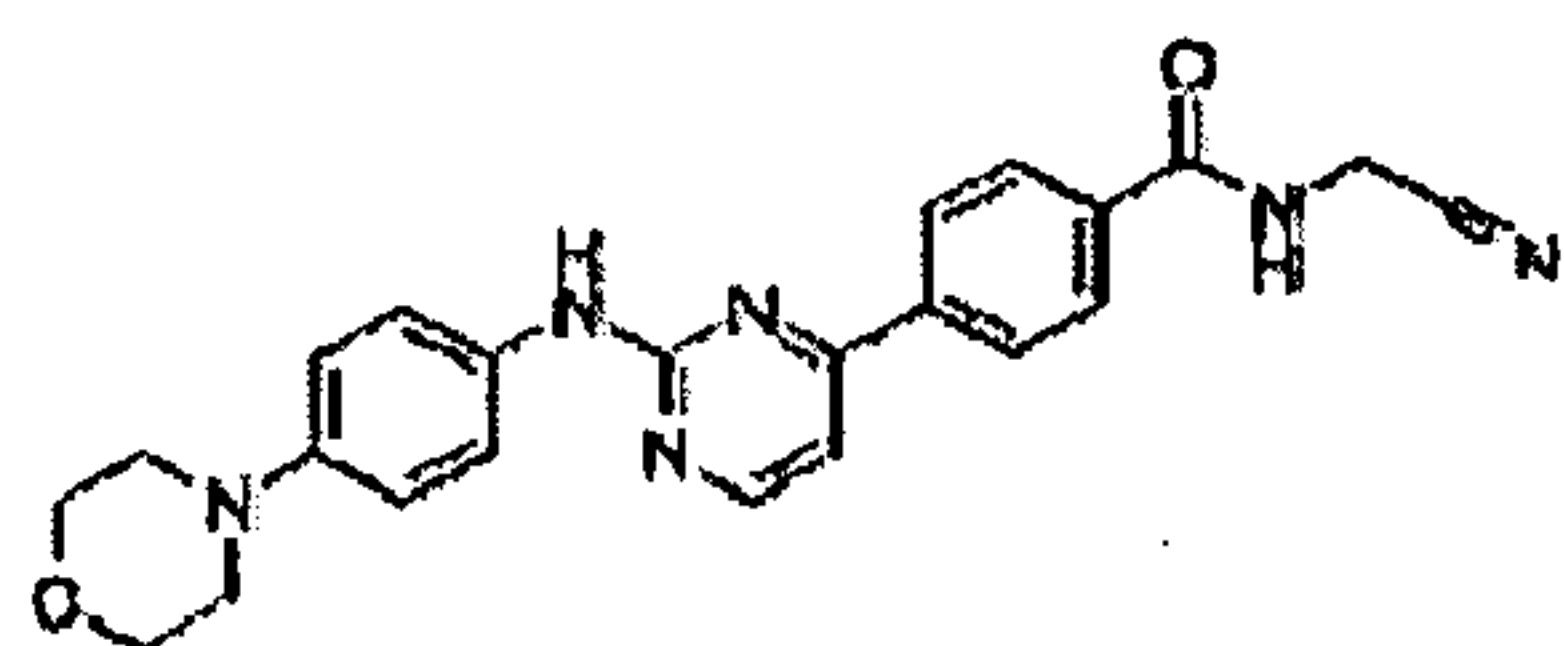
Ruxolitinib against JAK1/JAK2 for psoriasis, myelofibrosis, and rheumatoid arthritis is shown in the following formula:



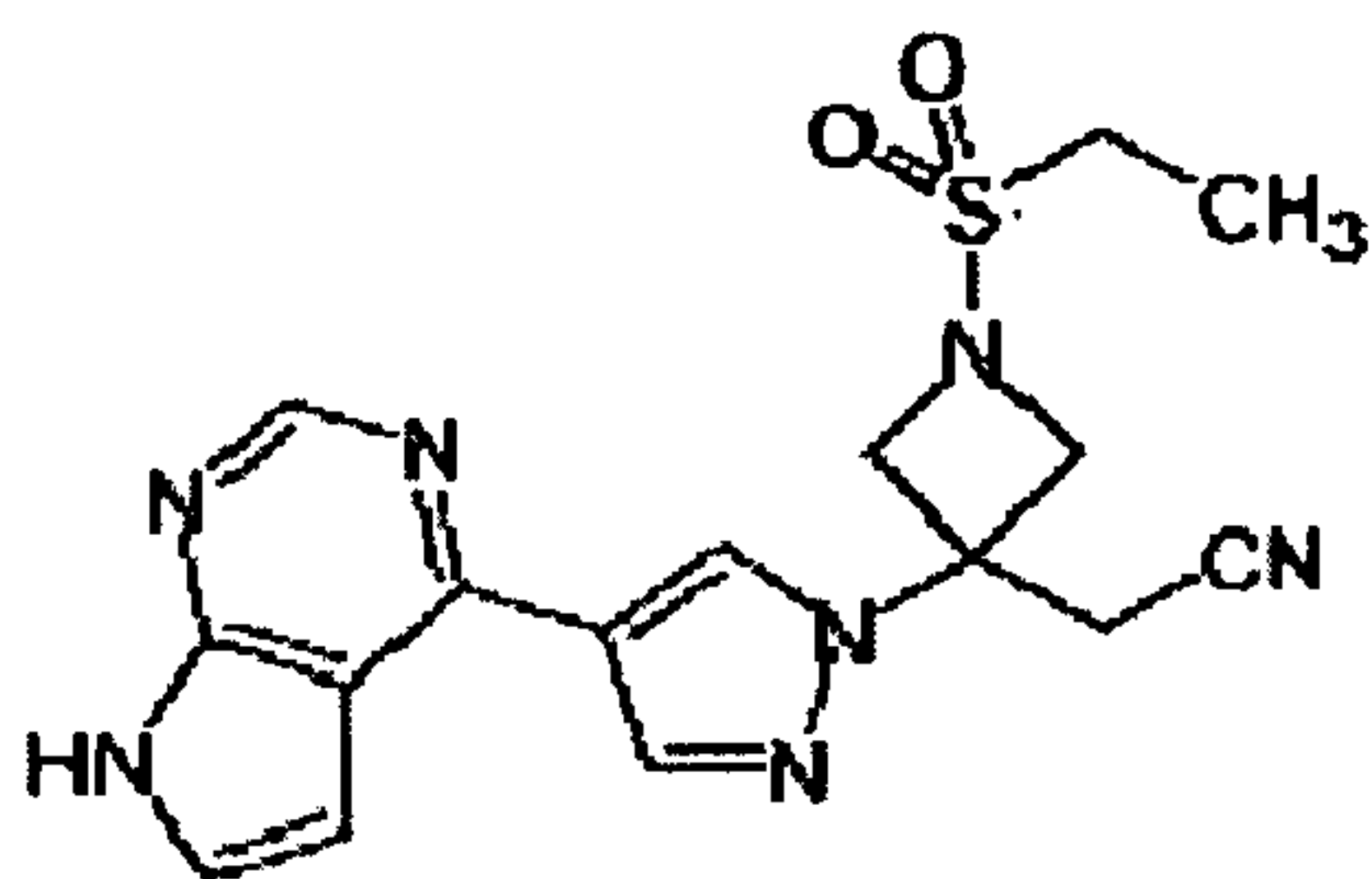
10 Pacritinib (SB1518) against JAK2 for relapsed lymphoma, advanced myeloid malignancies, myelofibrosis and CIMF Phase II results for polycythemia vera and thrombocythemia myelofibrosis is represented by the following formula:



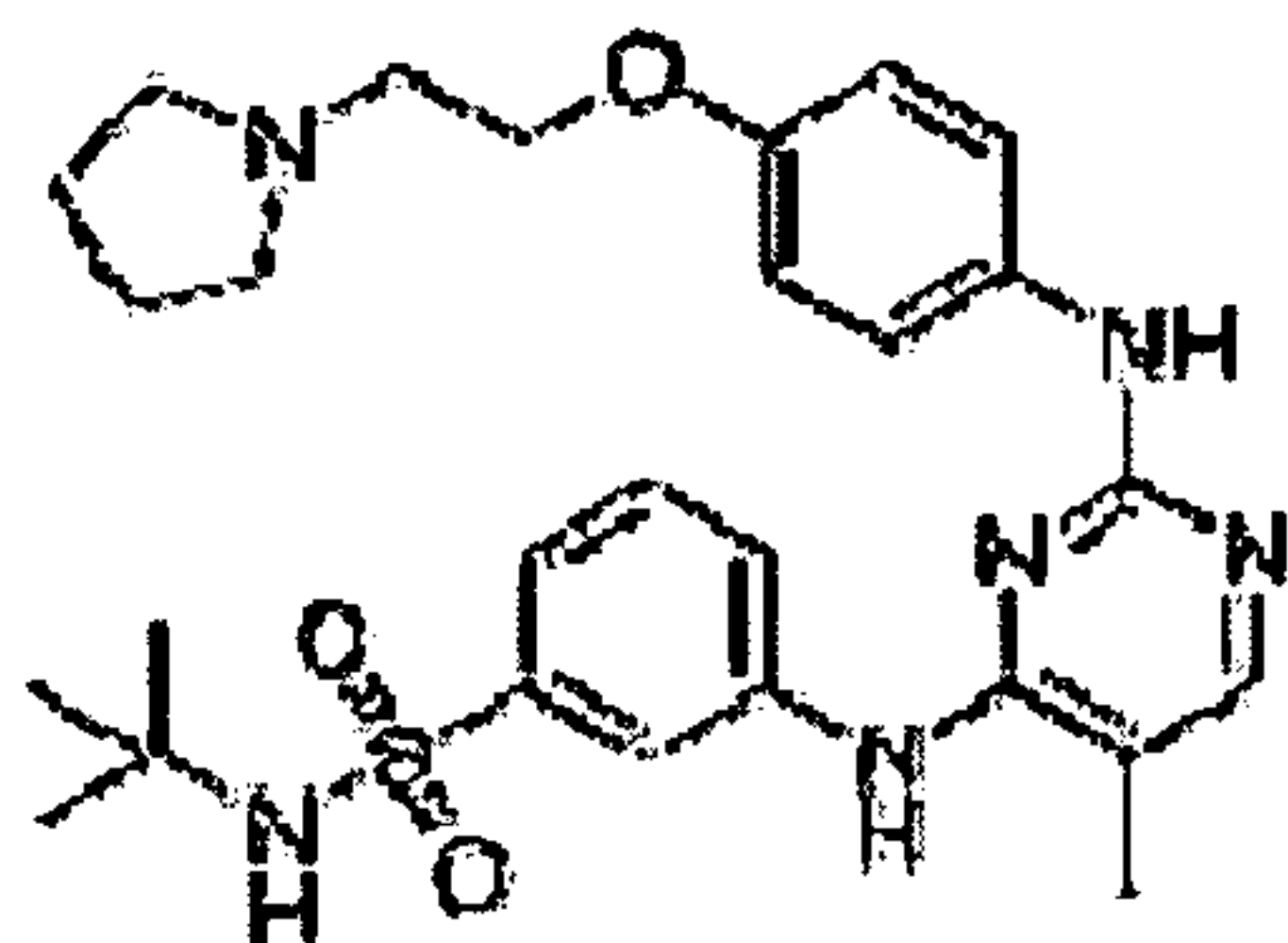
CYT387 against JAK2 for myeloproliferative disorders is shown in the following formula:



Baricitinib (LY3009104, INCB28050) against JAK1/JAK2 for rheumatoid arthritis is shown in the following formula.



TG101348 (SAR302503) is an orally available inhibitor of Janus kinase 2 (JAK-2) developed for the treatment of patients with myeloproliferative diseases including myelofibrosis. TG101348 acts as a competitive inhibitor of protein kinase JAK-2 with $IC_{50}=6$ nM; related kinases FLT3 and RET are also sensitive, with $IC_{50}=25$ nM and $IC_{50}=17$ nM, respectively. Significantly less activity was observed against other tyrosine kinases including JAK3 ($IC_{50}=169$ nM). In treated cells the inhibitor blocks downstream cellular signaling (JAK-STAT) leading to suppression of proliferation and induction of apoptosis. TG101348 is represented by the following formula:



In one embodiment of the present invention methods are provided for treating multiple sclerosis (MS) in a human in need thereof, comprising administering a STAT3 inhibitor to said human.

5 In one embodiment of the present invention, methods are provided for repositioning a pharmaceutical, comprising the steps of:

selecting at least one target gene, gene product, or loci associated with the treatment of at least one first disease, trait and/or phenotype by said pharmaceutical,

10 identifying at least one second disease, trait and/or phenotype associated with least one target gene, gene product, or loci of (a) using genome-wide associated studies,

selecting at least one second disease, trait and/or phenotype based on step (b) for treatment with said pharmaceutical.

15 In one aspect, the methods further comprise determining expression or overexpression and/or amplification of said first target gene, gene product, or loci in said second disease, trait and/or phenotype. In another aspect, the methods of the present invention further comprise identifying additional data and/or experimental support for target gene in said second disease, trait and/or phenotype. In another embodiment, the
20 methods comprise identifying at least one SNPs in said target gene in said second disease, trait and/or phenotype.

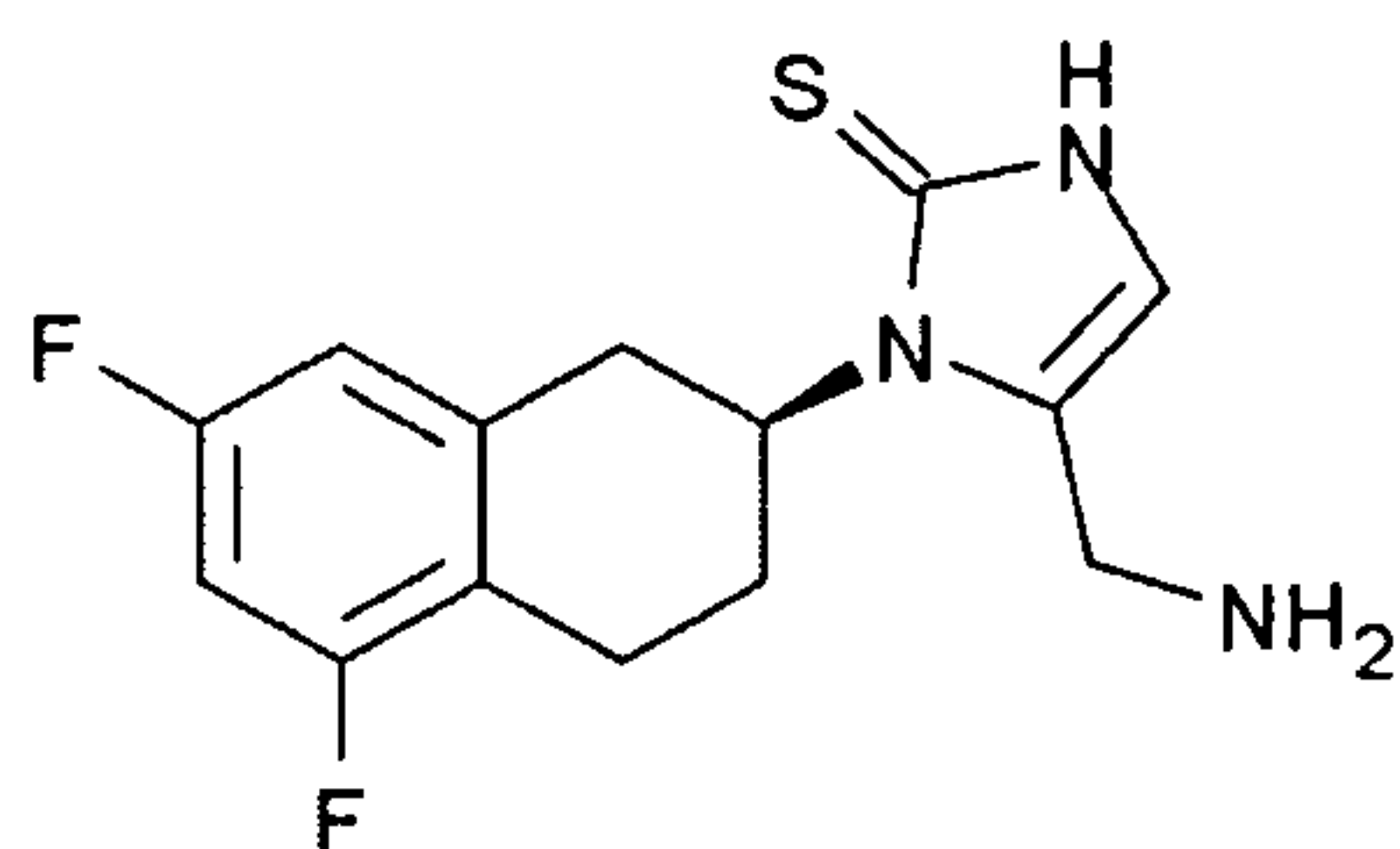
In another embodiment of the present invention, methods are provided for validating or invalidating a first therapeutic indication of a pharmaceutical comprising matching all GWAS associated diseases, traits and/or phenotypes of at least one target gene associated
25 with said first therapeutic indication and determining if at least one GWAS associated disease, trait and/or phenotype of said target gene is associated with said first therapeutic indication.

In another embodiment of the present invention, methods are provided for selecting a therapeutic agent for treatment or prevention of a disease comprising the steps of:

- selecting at least one target gene or gene product associated with at least one disease, trait and/or phenotype by at least one genome-wide associated study;
- 5 optionally determining if said target gene or gene product is small molecule druggable, secreted protein, antibody accessible, or modifiable by some other modality including anti-sense oligos, gene therapy, aptamers;
- determining if said target is under expressed or over expressed for a particular disease, trait and/or phenotype;
- 10 selecting a therapeutic agent that is an agonist to said target gene or gene product if said gene is under reduced functionality in said disease and/or trait of step (a) and selecting a therapeutic agent that is an antagonist to said target gene or gene product if said gene is under increased functionality in a particular disease and/or trait.

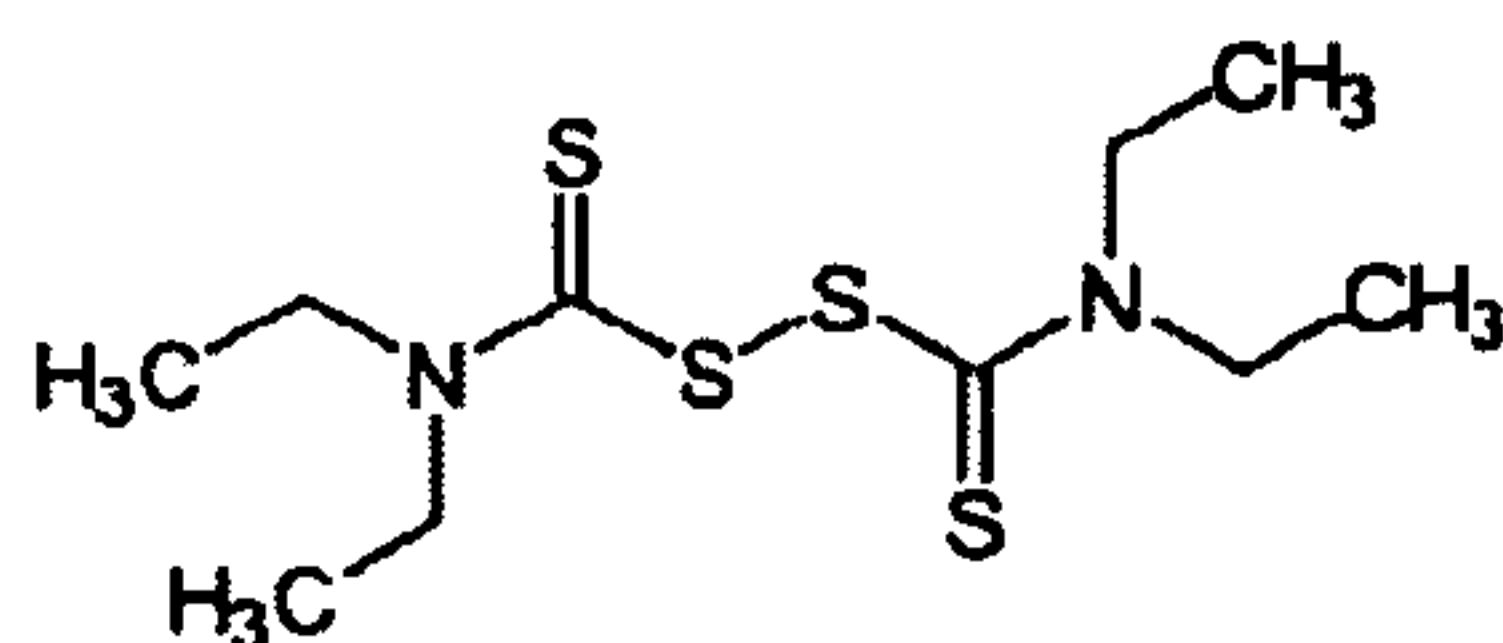
- 15 In another embodiment of the present invention, methods are provided for aiding a human to reduce the frequency of smoking or stop smoking cigarettes comprising administering a dopamine beta-hydroxylase inhibitor to said human. Inhibitors of dopamine beta-hydroxylase are described in US Patent Nos. 4,487,761 and 5,538,988 as well as US Patent Publication No. 20100105748. In some aspects, the dopamine beta-
- 20 hydroxylase inhibitor is Nepicastat®. In some aspects, the dopamine beta-hydroxylase inhibitor is disulfuram. In some aspects, the dopamine beta-hydroxylase inhibitor is selected from S-5-(aminomethyl)-1-[(2*S*)-5,7-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl]-1,3-dihydro-2*H*-imidazole-2-thione and 1,1',1'',1'''-[disulfanediy]bis(carbonothioyl nitrilo)]tetraethane or pharmaceutically acceptable salts
- 25 thereof.

Nepicastat® (5-(aminomethyl)-1-[(2*S*)-5,7-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl]-1,3-dihydro-2*H*-imidazole-2-thione) is an inhibitor of dopamine beta-hydroxylase, an enzyme that catalyzes the conversion of dopamine to norepinephrine. The chemical structure of Nepicastat® is shown below as Formula 1



1

Disulfiram (1,1',1'',1'''-[disulfanediy]bis(carbonothioylnitrilo)]tetraethane) is used to support the treatment of chronic alcoholism by producing an acute sensitivity to alcohol. Trade names for disulfiram in different countries are Antabuse® and Antabus®. The chemical structure of disulfiram is shown below as Formula 2



2

In another embodiment of the present invention, methods are provided for treating Type 1 diabetes in a human comprising administering IL2 or an IL2 mimetic to said human. In some instances, the IL2 or IL2 mimetic is selected from aldesleukin and Proleukin®.

Proleukin® is manufactured by Chiron Corporation of Emeryville, Calif. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by a serine residue (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from *E. coli*, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Pat. No. 4,931,543. The IL-2 formulation marketed as Proleukin is supplied as a sterile, white to off-white preservative-free lyophilized powder in vials containing 1.3 mg of protein (22 MIU).

Aldesleukin is a man-made protein that has the same actions as native human interleukin-2 (IL-2). Interleukins are the messengers by which white blood cells communicate with each other to coordinate inflammation and immunity. Among its actions, IL-2 increases the number and activities of certain types of white blood cells called lymphocytes, monocytes, and macrophages that are involved in inflammation and immunity. For example, lymphocytes fight viral infections, regulate the immune system,

and fight cancers. Aldesleukin is given only by injection. Aldesleukin was FDA approved in 1992.

In another embodiment of the present invention, methods are provided for treating Crohn's disease in a human, comprising administering an inhibitor and/or antagonist of tumor necrosis factor ligand, member 15, to said human. In one aspect the inhibitor and/or antagonist is a monoclonal antibody.

In another embodiment of the present invention, methods are provided for treating inflammatory bowel syndrome in a human comprising administering an inhibitor and/or antagonist of tumor necrosis factor ligand, member 15, to said human. In one aspect the inhibitor and/or antagonist is a monoclonal antibody.

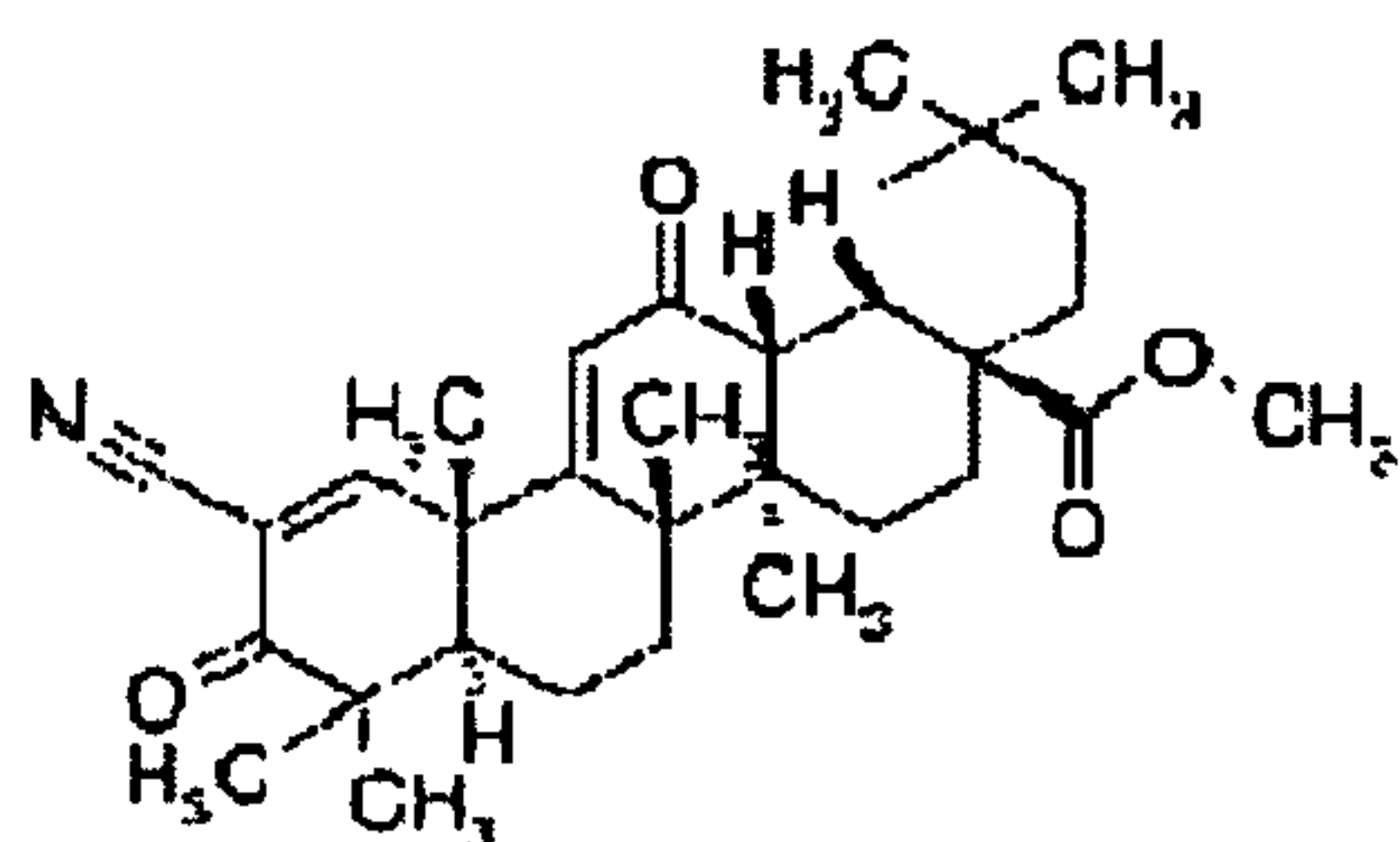
In another embodiment of the present invention, methods are provided for treating Crohn's disease in a human, comprising administering an inhibitor and/or antagonist of tumor necrosis factor ligand, member 11, to said human. In one aspect the inhibitor and/or antagonist is a monoclonal antibody. In one aspect the monoclonal antibody is denosumab.

Receptor activator of nuclear factor kappa-B ligand (RANKL), also known as tumor necrosis factor ligand superfamily member 11 (TNFSF11), TNF-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL), and osteoclast differentiation factor (ODF), is a protein that in humans is encoded by the *TNFSF11* gene. Critical for adequate bone metabolism, this surface-bound molecule (also known as CD254) found on osteoblasts serves to activate osteoclasts, which are the cells involved in bone resorption.

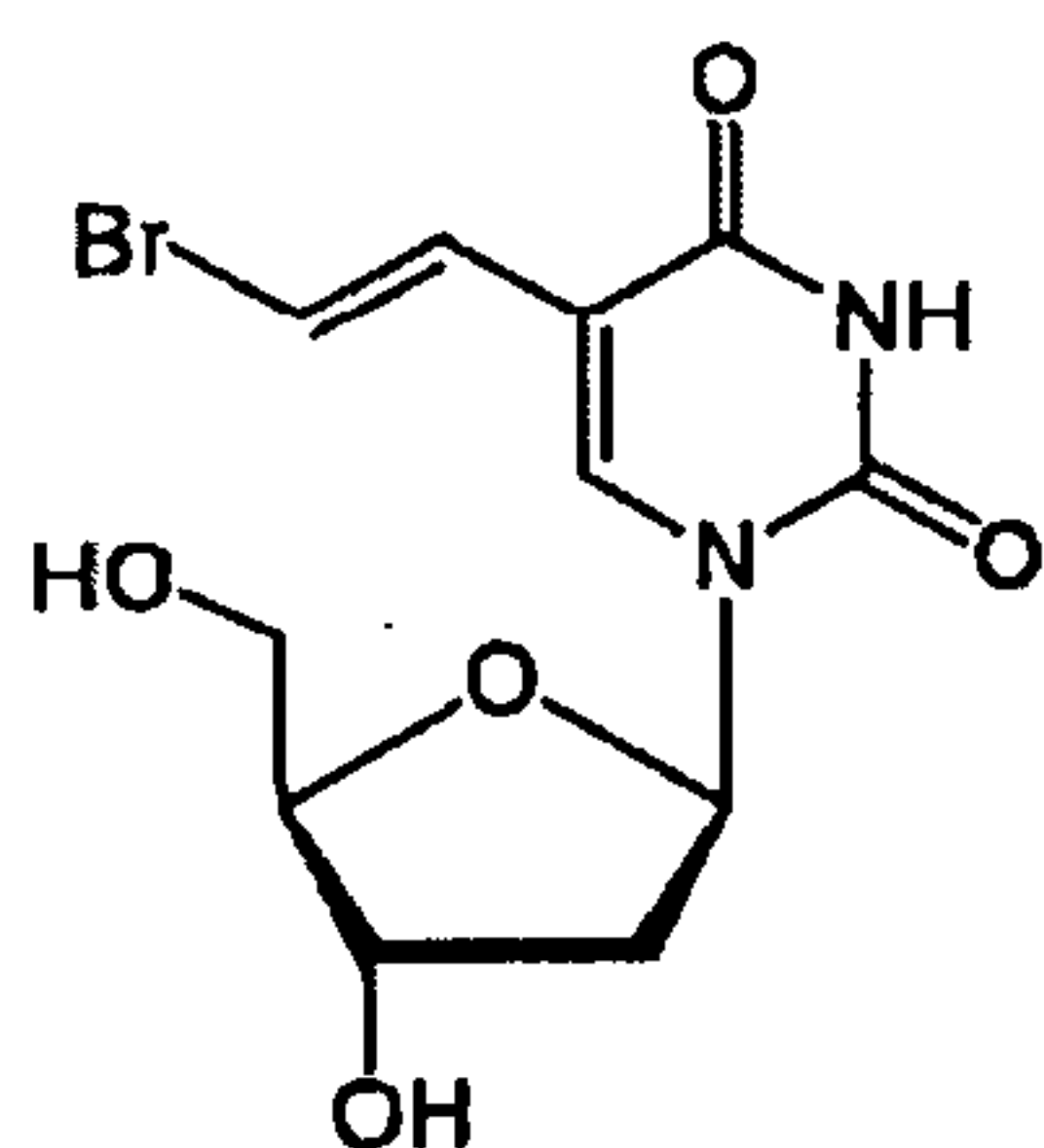
RANKL is a member of the tumor necrosis factor (TNF) cytokine family which is a ligand for osteoprotegerin and functions as a key factor for osteoclast differentiation and activation. RANKL also has a function in the immune system, where it is expressed by T helper cells and is thought to be involved in dendritic cell maturation. This protein was shown to be a dendritic cell survival factor and is involved in the regulation of T cell-dependent immune response. T cell activation was reported to induce expression of this gene and lead to an increase of osteoclastogenesis and bone loss. This protein was shown to activate antiapoptotic kinase AKT/PKB through a signaling complex involving SRC kinase and tumor necrosis factor receptor-associated factor 6 (TRAF6), which indicated this protein may have a role in the regulation of cell apoptosis.

STAT3 inhibitors include, but are not limited to, OPB-31121 (A Novel STAT3 Inhibitor OPB-31121 Induces Tumor-Specific Growth Inhibition in a Wide Range of Hematopoietic Malignancies without Growth Suppression of Normal Hematopoietic Cells 53rd ASH Annual Meeting and Exposition December , 2011 absrtact); OPB-51602 (Clinicaltrial.gov); Bardoxolone methyl; Brivudine, and RESprote. Various STAT3 inhibitors are described in US2011/0172429, US20110223661, US20110312,984, and US20120035114.

Bardoxolone methyl can be described by the following formula.



Brivudine can be described by the following formula.



In another embodiment of the present invention, methods are provided for treating Type II diabetes in a human comprising administering an agonist to melatonin receptor 1B to said human. In one aspect, said agonist is melatonin.

In another embodiment of the present invention, methods are provided for treating psoriasis in a human comprising administering to said human antagonist of interleukin 13. In one aspect, the antagonist is a monoclonal antibody to IL-13.

In another embodiment of the present invention, methods are provided for treating Behcet's disease in a human comprising administering an inhibitor and/or antagonist of IL-10 to said human. Monoclonal antibodies to human IL-10 are described in WO2011064399 and WO2011 064398.

In another embodiment of the present invention, methods are provided for treating essential tumor in a human, comprising administering an inhibitor to leucine rich repeat and Ig domain containing 1 (LINGO) to said human. In one aspect the inhibitor of the inhibitor of leucine rich repeat and Ig domain containing 1 (LINGO) is Biib-033.

5 In another embodiment of the present invention, methods are provided for treating Alzheimer's disease in a human comprising administering a compound that upregulates clusterin to said patient. In one aspect the compound that upregulates clusterin is selected from Valproate and Vorinostat.

10 Anti-clusterin antibodies and antigen binding fragment are described are described in WO2011063523.

In another embodiment of the present invention, methods are provided for treating Alzheimer's disease in a human comprising administering a compound that modulates complement component (3b/4b) receptor 1. In one aspect the compound that modulates complement component (3b/4b) receptor 1 is selected from Candida hp, CDx-1135, Eti-
15 204, and Eti-211.

In another embodiment of the present invention, methods are provided for treating Alzheimer's disease in a human comprising administering to said human a clusterin inhibitor. In one aspect the clusterin inhibitor is selected from Ab-16b5 and Clustirsen.

In another embodiment of the present invention, methods are provided for treating
20 Crohn's disease and/or Celiac disease in a human comprising administering a T-cell co-stimulatory ligand to said human. In one aspect the T-cell co-stimulator is an antibody that binds B7 related proteins. T-cell co-stimulators are described in US Patent Nos. 7,030,219 and 7,560,540, 7,101,550, 7,358,354, 7,723,479, 7,414,122, 7,595,048, 7,563,896, 7,488,802, and 7,432,351 as well as WO 2010/027828, WO 2010/098788, WO
25 2010/027423. In one aspect, the T-cell co-stimulator is AMG-557, which is a human antibody that binds to B7 related protein (B7RP-1).

In another embodiment of the present invention, methods are provided for treating Crohn's disease and/or inflammatory bowel disease (IBD) in a human comprising administering an IL-18 receptor antagonist and/or inhibitor to said human. In one aspect,
30 the IL-18R antagonist/inhibitor is a monoclonal antibody.

In another embodiment of the present invention, methods are provided for treating Crohn's disease and/or IBD in a human comprising administering an inducer of IL27

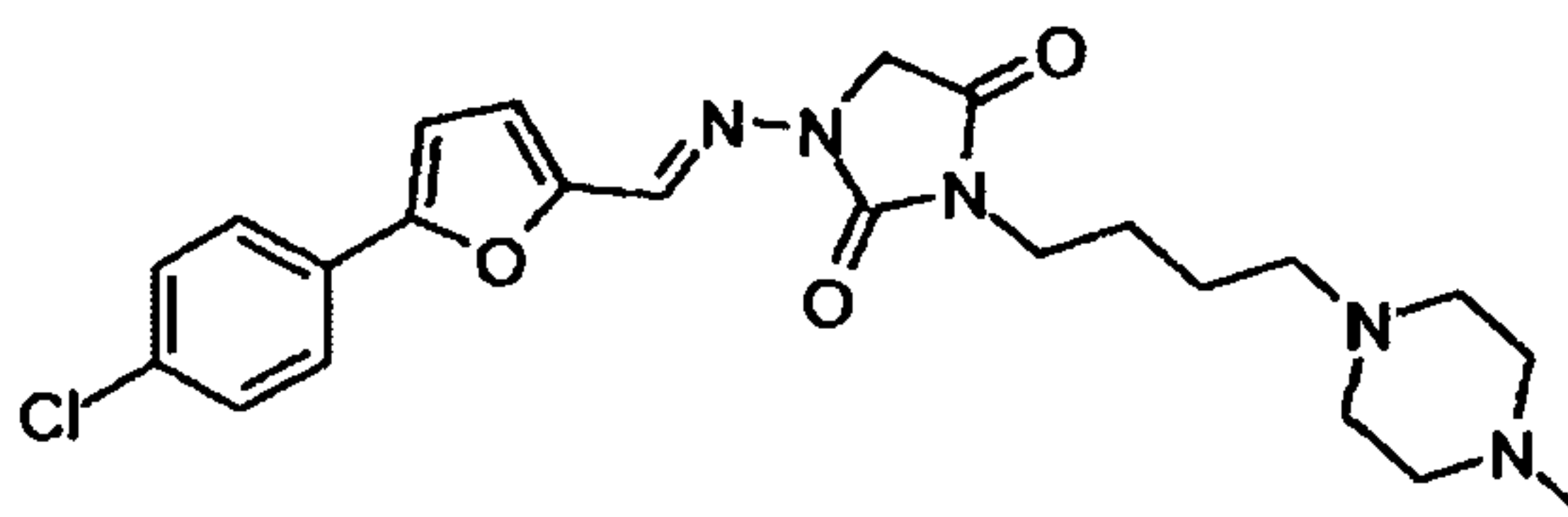
expression to said human. In one aspect, the inducer of IL27 expression is Rpi-78m. Methods of using Rpi-78m are described US Patent No. 8,034,777, titled "*Modified anticholinergic neurotoxins as modulators of the autoimmune reaction*," describes a composition of matter and method of its use for the treatment of multiple sclerosis in
5 humans. The composition is a modified anticholinergic alpha-neurotoxin.

In another embodiment of the present invention, methods are provided for treating primary biliary cirrhosis in a human comprising administering a compound that modulates IL12A to said human. In one aspect the compound that modulates IL12A is selected from briakinumab; ustekinumab, an IL-12 expressing plasmid, Egen-001; and Interleukin-12,
10 including HemaMax.

IL-12 antibodies are described in US Patent No. 7,887,807. EGEN-001 (E1), an IL-12 expressing plasmid formulated with a novel gene delivery system, stimulates natural killer cells, IFN- γ secretion, and T-helper 1 response, inhibits tumor neovascularization, and has potent antitumor activity in preclinical models of ovarian cancer.

15 In another embodiment of the present invention, methods are provided for treating Crohn's disease in a human comprising administering an anti-IL2 receptor mAb to said human.

In another embodiment of the present invention, methods are provided for treating Type II diabetes in a human comprising administering azimilide to said human. Azimilide
20 is a class III antiarrhythmic drug (used to control abnormal heart rhythms). The agents from this heterogeneous group have an effect on the repolarization, they prolong the duration of the action potential and the refractory period. Also they slow down the spontaneous discharge frequency of automatic pacemakers by depressing the slope of diastolic depolarization. They shift the threshold towards zero or hyperpolarize the
25 membrane potential. Although each agent has its own properties and will have thus a different function. Azilimide has the following chemical structure and IUPAC name:



1-((*E*)-[5-(4-chlorophenyl)furan-2-yl]methylidene)amino)-3-[4-(4-methylpiperazin-1-yl)butyl]imidazolidine-2,4-dione.

In another embodiment of the present invention, methods are provided for treating Type I diabetes in a human comprising administering ACN-189 and/or AEN-071 to said human.

In another embodiment of the present invention, methods are provided for treating systemic lupus erythematosus in a human comprising administering an inhibitor of TNFSF4 to said human. In one aspect the inhibitor of TNFSF4 is Oxelumab. Oxelumab is an IgG1 monoclonal antibody with human monoclonal γ -chain and human monoclonal κ -chain. Oxelumab binds to human antigen OX-40 ligand which is a member of Tumor Necrosis Factor Ligand superfamily, member 4.

In another embodiment of the present invention, methods are provided for treating coronary heart disease in a human comprising administering an CXCL12-specific inhibitor to said human. In one aspect the CXCL12-specific inhibitor is NOX-A12. NOX-A12 is an L: -enantiomeric RNA oligonucleotide.

In another embodiment of the present invention, methods are provided for treating idiopathic pulmonary fibrosis, comprising administering at least one telomerase reverse transcriptase inhibitor.

Examples of CCR4 inhibitors such as N-[(3-{[3-{[(5-Chloro-2-thienyl)sulfonyl]amino}-4-(methoxy)-1H-indazol-1-yl]methyl}phenyl)methyl]-2-hydroxy-2-methylpropanamide are described in WIPO international publication WO2010/097395 and US Patent Publication No. 20100216860 A1.

Examples of PDE4 inhibitors such as GSK-256066 (6-({3-[(dimethylamino)carbonyl]phenyl}sulfonyl)-8-methyl-4-{[3-methoxy]phenylamino}-3-quinolinecarboxamide) can be found in PCT/EP04/05494 - WIPO publication WO2004103998 A1 and US Patent Nos. 7,572,915 and 7,566,786 and GSK-356278 (5-(5-((2,4-dimethylthiazol-5-yl)methyl)-1,3,4-oxadiazol-2-yl)-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine) can be found in PCT/EP03/14867 - WIPO publication WO 2004056823 A1 and US Patent No. 7,528,148.

PTK2 protein tyrosine kinase 2 inhibitors (or FAK inhibitors) such as (2-((5-chloro-2-((1-isopropyl-3-methyl-1H-pyrazol-5-yl)amino)pyridin-4-yl)amino)-N-

methoxybenzamide) are described and claimed in PCT/US2009/062163 – WIPO Publication WO/2010/062578 and US Publication Nos. US 20100113475 A1 and US 20110269774 A1.

5 Examples of opoid receptor agonists such as GSK1521498 (N-((3,5-difluoro-3'-(4H-1,2,4-triazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-2,3-dihydro-1H-inden-2-amine) are described in PCT/US2007/075422 - WIPO publication WO 2008021849 A2 and US Publication No. US 20100113512 A1.

10 Examples of antibodies that bind and neutralize NOGO such as GSK-1223249 are described in US Patent Nos. 7,780,964 and 7,988,964. Antibodies and single chain antibodies that bind NOGO receptor are described in US Patent No. 7,973,139.

"NOGO" refers to any NOGO polypeptide, including variant forms. This includes, but is not limited to, NOGO-A having 1192 amino acid residues (GenBank accession no. AJ251383); NOGO-B, a splice variant which lacks residues 186 to 1004 in the putative extracellular domain (GenBank accession no. AJ251384) and a shorter splice variant, NOGO-C, which also lacks residues 186 to 1004 and also has smaller, alternative amino terminal domain (GenBank accession no. AJ251385) (Prinjha R et al (2000) Nature 403, 383-384; Chen MS et al (2000) Nature 403). All references to "NOGO" herein is understood to include any and all variant forms of NOGO such as NOGO-A and the splice variants described, unless a specific form is indicated.

20 In another embodiment of the present invention, new therapeutic indications are provided for drugs and biotherapeutics according to Table 1. The column designated "New suggested indication" of the Table 1 provides new therapeutic indication determined by the methods of the present invention for the corresponding drugs and classes of therapy listed in the column designated "All drugs" of Table 1.

25

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Coronary heart disease	78	rs2515629-A (0.78)	Coronary heart disease	Alzheimer's disease; Atherosclerosis; Cholelithiasis; Diabetes, Type 2; Hyperlipidaemia, general; Steatohepatitis
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Dialysis-related mortality	31	rs17110736-? (0.35)	Dialysis-related mortality	Macular degeneration, early onset
ACHE	acetylcholinesterase	Type 2 diabetes	61	rs7636-A (0.06)	Type 2 diabetes	Alzheimer's disease; Arthritis, osteo; Arthritis, rheumatoid; Attention deficit hyperactivity disorder; Cognitive disorder, unspecified; Dementia, Lewy body; Dementia, Parkinson's disease; Dementia, presenile; Dementia, senile, general; Dementia, vascular; Depression, general; Down's syndrome; Dyspepsia; Fibromyalgia; Gastritis; Huntington's disease; Ischaemia, cerebral; Migraine; Motility dysfunction, GI, general; Poisoning, organophosphate; Radio/chemotherapy-induced injury, general; Schizophrenia; Urinary retention
ACVR2A	activin A receptor, type IIA	Response to statin therapy	75	rs7584099-G (0.41)	Response to statin therapy	Anaemia, radio/chemotherapy-induced; Anaemia, renal disease-induced; Cancer, bone; Cancer, general; Cancer, myeloma; Osteoporosis
						All drugs
						Alzheimer's disease therapy, Madera BioSciences; Aramchol; RG-72
						StarG
						60714; GLN-1062; KW-5092; NP-0361; P26; TAK-802; Yissum Project No. B-1045; Acetylcholinesterase, Protalix; Acotiamide hydrochloride; Donepezil hydrochloride; Donepezil hydrochloride RDT; Donepezil hydrochloride jelly; Donepezil hydrochloride, APR; Donepezil hydrochloride, SR; Donepezil transdermal patch; Eptastigmine; Galantamine hydrobromide; Galantamine, CR capsule; Huperzine A; Itopride hydrochloride; Ladostigil tartrate; Memantine + donepezil, Adamas; Methanesulfonyl fluoride, Senexta; Metrifonate; Mimosipil; Mimosipil LA; Mimosipil, implant; Physostigmine, Forest; Physostigmine, Klinge; Rivastigmine tartrate; Rivastigmine tartrate, TDS; Tacrine; Tacrine, OROS; Thiatolseri
						EDF, Ajinomoto; Sotaterce

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
ADRA2A	adrenergic, alpha-2A-, receptor	Fasting glucose-related traits	18	rs10885122-G (0.87)	Fasting glucose-related traits	Addiction, narcotic/opiate; Anxiety, general; Apnoea; Attention deficit hyperactivity disorder; Conjunctivitis, inflammatory; Depression, general; Depression, major depressive disorder; Dyskinesia, general; Dyskinesia, levodopa-induced; Fibromyalgia; Glaucoma; Heart failure; Hypertension, general; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Neuropathy, diabetic; Obsessive-compulsive disorder; Pain, cancer; Pain, general; Pain, neuropathic; Panic disorder; Parkinson's disease; Post-traumatic stress disorder; Radio/chemotherapy-induced mucositis; Retinal detachment; Retinitis pigmentosa; Surgery adjunct	ADX-415; Brimonidine-DDS; Org-4419; Parkinson's therapy, Heptares; Bimatoprost/brimonidine tartrate/timolol; Brimonidine; Brimonidine + timolol; Allergan; Brimonidine tartrate, Eye Therapies; Brinzolamide + brimonidine, Alcon; Clonidine ER, once-daily, Tris Pharma; Clonidine SR, Addrenex; Clonidine, Alza; Clonidine, BioAlliance Pharma; Clonidine, Biovail; Clonidine, Fujisawa; Clonidine, Hisamitsu; Clonidine, Jazz; Clonidine, topical, Arcion; Dorzolamide HCl/brimonidine tartrate/timolol, Allergan; Fipamezole; Guanfacine; Guanfacine carrierwave; Guanfacine, ER, Shire; Lofexidine; Mirtazapine; Mirtazapine, immediate-release; Prazosin; Prazosin, AI
AHR	aryl hydrocarbon receptor	Coffee consumption	3	rs6968865-T (0.593)	Coffee consumption	Cancer, solid, general	5F-DF-2
AKT3	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	RR interval	4	rs4132509-A (0.21)	RR interval	Cancer, solid, general	LY-25030
AKT3	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	Diabetic retinopathy	34	rs10927101-A (0.38), rs476141-A (0.51)	Diabetic retinopathy	Cancer, solid, general	LY-25030
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Esophageal cancer	15	rs671-A (NR)	Esophageal cancer	Alcohol intolerance	Fomepizole, Rapt
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Upper aerodigestive tract cancers	7	rs4767364-A (0.29)	Upper aerodigestive tract cancers	Alcohol intolerance	Fomepizole, Rapt

Table 1		Strongest			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)			
APOA1	apolipoprotein A-I	Coronary heart disease	78	rs964184-G (0.13)	Coronary heart disease	Acute coronary syndrome; Alzheimer's disease; Angina, general; Atherosclerosis; Hypercholesterolaemia; Hyperlipidaemia, general; Ischaemia, general; Restenosis; Sepsis; Stenosis, aortic valve	48266; CER-001; CER-522; CRD-5; CRD-510; ET-216; ET-642; QRS-10-001; QRS-5-005; RVX-208; RVX-408; Rev-D4F; Apolipoprotein A-I upregulators, GlaxoSmithKline; Apolipoprotein A1 + interferon alfa-5, Digna Biotech; Apolipoprotein AI, SemBioS
APOB	apolipoprotein B (including Ag(x) antigen)	Erectile dysfunction and prostate cancer treatment	23	rs219553-? (0.42)	Erectile dysfunction and prostate cancer treatment	Atherosclerosis; Hypercholesterolaemia	49694; BI-204; PRO-040201; SPC-4955; MiApoB10, Amsterdam Molecular Therapeutics; Mipomersen sodium; ShApoB
APOB	apolipoprotein B (including Ag(x) antigen)	Response to statin therapy	75	rs541041-G (0.16)	Response to statin therapy	Atherosclerosis; Hypercholesterolaemia	49694; BI-204; PRO-040201; SPC-4955; MiApoB10, Amsterdam Molecular Therapeutics; Mipomersen sodium; ShApoB
APOB	apolipoprotein B (including Ag(x) antigen)	Hypertriglyceridemia	5	rs4635554-G (0.31)	Hypertriglyceridemia	Atherosclerosis; Hypercholesterolaemia	49694; BI-204; PRO-040201; SPC-4955; MiApoB10, Amsterdam Molecular Therapeutics; Mipomersen sodium; ShApoB
APOC3	apolipoprotein C-III	Coronary heart disease	78	rs964184-G (0.13)	Coronary heart disease	Hyperlipidaemia, general	ISIS-APOCIII
APOE	apolipoprotein E	Longevity	23	rs2075650-A (0.74)	Longevity	Acute coronary syndrome; Alzheimer's disease; Colitis, general; Hypercholesterolaemia; Multiple sclerosis, general; Multiple sclerosis, progressive, general; Multiple sclerosis, relapsing-remitting; Spinal cord injury	AEM-18; AEM-28; Alzheimer's disease therapy, Madera BioSciences; COG-112; Apolipoprotein-E2, GlaxoSmith
APOE	apolipoprotein E	Alzheimer's disease	28	rs157580-? (NR), rs2075650-? (0.15), rs2075650-? (0.90), rs2075650-G (0.14), rs2075650-G (0.20), rs4420638-? (NR), rs6859-A (NR)	Alzheimer's disease	Acute coronary syndrome; Alzheimer's disease; Colitis, general; Hypercholesterolaemia; Multiple sclerosis, general; Multiple sclerosis, progressive, general; Multiple sclerosis, relapsing-remitting; Spinal cord injury	AEM-18; AEM-28; Alzheimer's disease therapy, Madera BioSciences; COG-112; Apolipoprotein-E2, GlaxoSmith

Table 1								
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)		New suggested indication	Current indications	All drugs
APOE	apolipoprotein E	Alzheimer's disease biomarkers	4	rs429358-? (NR)		Alzheimer's disease biomarkers	Acute coronary syndrome; Alzheimer's disease; Colitis, general; Hypercholesterolaemia; Multiple sclerosis, general; Multiple sclerosis, progressive, general; Multiple sclerosis, relapsing-remitting; Spinal cord injury	AEM-18; AEM-28; Alzheimer's disease therapy, Madera BioSciences; COG-112; Apolipoprotein-E2, GlaxoSmith

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
AR	androgen receptor	LDL cholesterol	42	rs5031002-A (0.02)
				LDL cholesterol
				Current indications
				All drugs
				11096; 52649; 54962; 60003; ADR-L09; APC-100; ASP-9521; BLACE; CH-4933468; CH-5137291; CNF-316 series; DHEA + acolbifene, Endoceutics; EZN-4176; GLPG-0492; GTx-027; HE-3235; LGD-4033; LPCN-1098; LY-2452473 + tadalafil, Lilly; MDV-3100; ODM-201; PA-109; PS-178990; Permixon, once-daily, Pierre; Pharmaprojects No. 1381; Pharmaprojects No. 3606; RAD-140; SARD programme, Aragon; SARMS, GTx-2; VAL-201; ZD-3980; Abarelix; Androgen antagonists, BMS-2; Androgen inhibitor, AndroBio; Androgen receptor antagonists, BMS-3; Bicalutamide; Chlormadinone acetate + ethinyl estradiol; Contraceptive, BioSante; Cortodoxone; Cyproterone acetate + estradiol valerate, Bayer; Cyproterone acetate + ethinylestradiol, Douglas; Dehydroepiandrosterone, Bayer; Dehydroepiandrosterone, Endoceutics; Dihydrotestosterone, Unimed; Enclomiphene citrate; Flutamide; Galeterone; Nilutamide; Ostarine; Oxandrolone; Oxendolone; Oxymetholone, Unimed; Prostate cancer siRNA, SeleXel; Selective androgen receptor modulators, GTx; Sodium prasterone sulfate, S-P; Testosterone enanthate; Testosterone gel (intranasal, low-dose), Trimel BioPharma; Testosterone gel, Antares-2; Testosterone gel, Trimel BioPharma; Testosterone ophthalmic solution, Allergan; Testosterone patch, female; Testosterone transdermal, ProStrakan; Testosterone undecanoate, Bayer; Testosterone undecanoate, Clarus; Testosterone, Acrux-1; Testosterone, Acrux-2; Testosterone, Alza; Testosterone, Antares; Testosterone, Auxilium; Testosterone, Auxilium-2; Testosterone, Cortecs; Testosterone, Lipocine; Testosterone, Pierre Fabre; Testosterone, Savient; Testosterone, TheraTech; Testosterone, Unimed; Testosterone, Watson, 2nd-generation; Testosterone, buccal, Columbia; Testosterone, vaginal, Columbia; Tibolo

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
ARSB	arylsulfatase B	Hippocampal atrophy	18	rs337847-? (NR)	Hippocampal atrophy	Fibrosis, general; Mucopolysaccharidosis VI
BCHE	butyrylcholinesterase	Heart failure	16	rs1523288-? (0.65)	Heart failure	Alzheimer's disease; Dementia, Parkinson's disease; Dementia, senile, general; Poisoning, drug; Poisoning, organophosphate
BMP2	bone morphogenetic protein 2	Body mass index	70	rs2145270-T (0.65)	Body mass index	Bone disorder, general; Bone fracture healing; Osteonecrosis; Osteoporosis; Regeneration, bone, spinal fusion; Regeneration, cartilage
BMP7	bone morphogenetic protein 7	Response to citalopram treatment	5	rs6127921-? (0.81), rs6127921-? (0.82)	Response to citalopram treatment	Arthritis, osteo; Bone fracture healing
						All drugs
						IBT-9402; Galsulfa
						NP-0361; Bisnorcymserine; Butyrylcholinesterase, PharmAt; Butyrylcholinesterase, Shire; Rivastigmine tartrate; Rivastigmine tartrate, T
						BMP gene therapy, Wyeth; Diboterminal alfa; RhBMP-2, Scil Technology-2; RhBPM-2/C
						Eptoterminal

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest
				SNP-Risk Allele (frequency)
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	Bipolar disorder and major depressive disorder	9	rs1006737-A (0.36)
				Bipolar disorder and major depressive disorder
				Anal fissure; Angina, general; Angina, unstable; Arrhythmia, general; Atherosclerosis; Cardiomyopathy, ischaemic; Enuresis; Epilepsy, general; Fibrillation, atrial; Gastritis; Haemorrhage, subarachnoid; Heart failure; Hypertension, general; Incontinence, urinary; Irritable bowel syndrome; Ischaemia, cerebral; Neurogenic bladder; Overactive bladder; Peripheral vascular disease; Pollakisuria; Shock, traumatic; Tachycardia, supraventricular
				(S)-amlodipine, Emcure; BRL-32872; F-0401; NS-3601; PCA-50941; R-verapamil, Celltech; S-2150; SK-310; SL-87-0495; Aliskiren + amlodipine + HCTZ, Novartis; Aliskiren + amlodipine, Novartis; Amlodipine; Amlodipine + benazepril; Amlodipine + irbesartan, Sanofi; Amlodipine + losartan + HCTZ, Merck; Amlodipine + losartan + hydrochlorothiazide, Hanmi; Amlodipine + losartan, HanAll; Amlodipine + metoprolol XL, AZ; Amlodipine + rosuvastatin, HanAll; Amlodipine + simvastatin, HanAll; Amlodipine + valsartan, Novartis; Amlodipine besilate + irbesartan, Dainippon; Amlodipine camsylate; Amlodipine maleate, SK; Amlodipine+HCTZ+valsartan, Nov; Amlodipine+losartan, Hanmi; Amlodipine, SUITAB; Aranidipine; Atenolol + nifedipine; Atorvastatin calcium + amlodipine; Azelnidipine; Benidipine hydrochloride; Bepridil; Bisaramil; Budralazine; Buflomedil; Candesartan cilexetil + amlodipine, Takeda; Cilnidipine; Cilnidipine + valsartan; Clevidipine butyrate; Delapril+manidipine, Chiesi; Diltiazem; Diltiazem SR, Ethypharm; Diltiazem hydrochloride, SLA; Diltiazem once-daily, Bago; Diltiazem once-daily, Biov; Diltiazem once-daily, Elan; Diltiazem once-daily, Biovail-2; Diltiazem twice-daily, Elan; Diltiazem, Alza; Diltiazem, Diffutab; Diltiazem, Douglas; Diltiazem, Edmond Pharma; Diltiazem, GEOMATRIX; Diltiazem, SURECAPS; Diltiazem, Watson; Diltiazem, Watson, PPDS; Diltiazem, Watson, SMHS; Diltiazem, once-daily, Mundipharma; Diltiazem, once-daily, Sanofi; Diltiazem, once-daily, Verex; Efonidipine; Enalapril + diltiazem, Biovail; Enalapril + nitrendipine, Vita; Fantofarone; Felodipine; Felodipine + enalapril; Felodipine + metoprolol; Felodipine + ramipril; Gallopamil; Hydralazine + ISDN; Hydralazine + magnesium valproate; Neolpharma; Irbesartan;

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	Bipolar disorder and major depressive disorder	9	rs1006737-A (0.36)
Continued				
			</	

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	Bipolar disorder	21	rs1006737-A (0.32)	Bipolar disorder	Anal fissure; Angina, general; Angina, unstable; Arrhythmia, general; Atherosclerosis; Cardiomyopathy, ischaemic; Enuresis; Epilepsy, general; Fibrillation, atrial; Gastritis; Haemorrhage, subarachnoid; Heart failure; Hypertension, general; Incontinence, urinary; Irritable bowel syndrome; Ischaemia, cerebral; Neurogenic bladder; Overactive bladder; Peripheral vascular disease; Pollakisuria; Shock, traumatic; Tachycardia, supraventricular	(S)-amlodipine, Emcure; BRL-32872; F-0401; NS-3601; PCA-50941; R-verapamil, Celltech; S-2150; SK-310; SL-87.0495; Aliskiren + amlodipine + HCTZ, Novartis; Aliskiren + amlodipine, Novartis; Amlodipine; Amlodipine + benazepril; Amlodipine + irbesartan, Sanofi; Amlodipine + losartan + HCTZ, Merck; Amlodipine + losartan + hydrochlorothiazide, Hanmi; Amlodipine + losartan, HanAll; Amlodipine + metoprolol XL, AZ; Amlodipine + rosuvastatin, HanAll; Amlodipine + simvastatin, HanAll; Amlodipine + valsartan, Novartis; Amlodipine besilate + irbesartan, Dainippon; Amlodipine camsylate; Amlodipine maleate, SK; Amlodipine+HCTZ+valsartan, Nov; Amlodipine+losartan, Hanmi; Amlodipine, SUITAB; Aranidipine; Atenolol + nifedipine; Atorvastatin calcium + amlodipine; Azelnidipine; Benidipine hydrochloride; Bepridil; Bisaramil; Budralazine; Buflomedil; Candesartan cilexetil + amlodipine, Takeda; Cilnidipine; Cilnidipine + valsartan; Clevidipine butyrate; Delapril+manidipine, Chiesi; Diltiazem; Diltiazem SR, Ethypharm; Diltiazem hydrochloride, SLA; Diltiazem once-daily, Bago; Diltiazem once-daily, Biov; Diltiazem once-daily, Elan; Diltiazem once-daily,Biovail-2; Diltiazem twice-daily, Elan; Diltiazem, Alza; Diltiazem, Diffutab; Diltiazem, Douglas; Diltiazem, Edmond Pharma; Diltiazem, GEOMATRIX; Diltiazem, SURECAPS; Diltiazem, Watson; Diltiazem, Watson, PPDS; Diltiazem, Watson, SMHS; Diltiazem, once-daily, Mundiph; Diltiazem, once-daily, Sanofi; Diltiazem, once-daily, Verex; Efonidipine; Enalapril + diltiazem, Biovail; Enalapril + nitrendipine, Vita; Fantofarone; Felodipine; Felodipine + enalapril; Felodipine + metoprolol; Felodipine + ramipril; Gallopamil; Hydralazine + ISDN; Hydralazine + magnesium valproate; Neolpharma; Irbesartan;	

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
CACNA1C Continued	calcium channel, voltage- dependent, L type, alpha 1C subunit	Bipolar disorder	21		rs1006737-A (0.32)	Bipolar disorder	Anal fissure; Angina, general; Angina, unstable; Arrhythmia, general; Atherosclerosis; Cardiomyopathy, ischaemic; Enuresis; Epilepsy, general; Fibrillation, atrial; Gastritis; Haemorrhage, subarachnoid; Heart failure; Hypertension, general; Incontinence, urinary; Irritable bowel syndrome; Ischaemia, cerebral; Neurogenic bladder; Overactive bladder; Peripheral vascular disease; Pollakisuria; Shock, traumatic; Tachycardia, supraventricular	amlodipine, HanAll; Isradipine; Isradipine, OROS; Lacidipine; Lemildipine; Lercanidipine; Lercanidipine + enalapril, Recordati; Lercanidipine + valsartan, LG Life Sciences; Lercanidipine immediate release; Lercanidipine, MeltDose; Manidipine; Mibefradil dihydrochloride; Nicardipine; Nifedipine; Nifedipine + candesartan, Bayer; Nifedipine once daily, Watson; Nifedipine twice-daily, Watson; Nifedipine, Alza; Nifedipine, Elan; Nifedipine, EnSoTrol; Nifedipine, Mundipharma; Nifedipine, Nippon Organon; Nifedipine, SURECAPS; Nifedipine, Siegfried; Nifedipine, TIMERx; Nilvadipine; Nimodipine; Nimodipine + endothelin antagonist, Edge; Nimodipine, Edge; Nisoldipine; Nisoldipine, SkyePharma; Nitrendipine; Olmesartan + amlodipine + HCTZ, Daiichi; Olmesartan + amlodipine, Daiichi Sankyo; Olmesartan + azelnidipine, Sankyo; Otilonium bromide; Phenytoin, Medisperse; Phenytoin, OROS; Phenytoin, Sirius; Pinaverium bromide; Pinaverium bromide + simethicone, Nycomed; Propiverine hydrochloride; S-amlodipine/telmisartan, Chong Kun Dang; Telmisartan + amlodipine, BI; Telmisartan + lacidipine, Glax; Tiapamil; Trandolapril + verapamil, Aven; Verapamil SR, Ethypharm; Verapamil, Eisai; Verapamil, Elan; Verapamil, Mylan; Verapamil, OROS, Alza; Verapamil, Orion-Farmos; Verapamil, Ver
CACNA2D 1	calcium channel, voltage- dependent, alpha 2/delta subunit 1	Non-alcoholic fatty liver disease histology	16		rs10954668-A (0.33)	Non-alcoholic fatty liver disease histology	Amyotrophic lateral sclerosis; Epilepsy, general; Epilepsy, partial (focal, local); Fibromyalgia; Generalized anxiety disorder; Inflammation, urinary tract; Insomnia; Menopausal symptoms, unspecified; Migraine prophylaxis; Neuropathy, diabetic; Pain, complex regional; Pain, general; Pain, musculoskeletal, general; Pain, neuropathic; Pain, post-herpetic; Pain, post-operative; Psychosis, bipolar; Restless legs syndrome; Sexual dysfunction, female; Social anxiety disorder	NPRx-10; PD-299685; PF-4480682; Atagabalin; Gabapentin; Gabapentin + cobalamin + thiamine; Gabapentin AcuForm, Dep; Gabapentin enacarbil; Gabapentin+oxybutynin,Dynogen; Gabapentin, Medtronic; Imagabalin; Pregabalin; Pregabalin, Protect; Pregabalin, controlled-relea

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
CBLB	Cas-Br-M (murine) ecotropic retroviral transforming sequence b	Multiple sclerosis	59	rs9657904-T (0.826)	Multiple sclerosis	Cancer, general
CCL2	chemokine (C-C motif) ligand 2	Crohn's disease	83	rs3091315-A (0.72)	Crohn's disease	Arthritis, rheumatoid; Asthma; Cancer, melanoma; Cancer, neuroendocrine, general; Cancer, ovarian; Cancer, prostate; Cancer, solid, general; Fibrosis, pulmonary, idiopathic; Hypertriglyceridaemia; Lupus nephritis; Nephropathy, diabetic; Psoriasis; Restenosis
CCR1	chemokine (C-C motif) receptor 1	Celiac disease	65	rs13098911-A (0.10), rs6441961-A (0.30)	Celiac disease	Arthritis, rheumatoid; Chronic obstructive pulmonary disease; Diabetes, Type 2; Lupus nephritis; Multiple sclerosis, general; Nephropathy, diabetic; Radio/chemotherapy-induced injury, bone marrow, general
CCR2	chemokine (C-C motif) receptor 2	Celiac disease	65	rs13098911-A (0.10)	Celiac disease	Arthritis, rheumatoid; Atherosclerosis; Bronchiectasis; Chronic obstructive pulmonary disease; Diabetes, Type 2; Fibrosis, liver; Hepatic dysfunction, general; Infection, HIV/AIDS; Multiple sclerosis, general; Nephropathy, diabetic; Pain, general; Pain, musculoskeletal, general; Pain, neuropathic; Periodontitis; Restenosis; Transplant rejection, general
CCR3	chemokine (C-C motif) receptor 3	Celiac disease	65	rs13098911-A (0.10), rs6441961-A (0.30)	Celiac disease	Asthma; Chronic obstructive pulmonary disease; Rhinitis, allergic, general; Rhinitis, general
CCR4	chemokine (C-C motif) receptor 4	Celiac disease	65	rs13314993-C (0.46)	Celiac disease	Asthma; Cancer, lymphoma, T-cell; Cancer, lymphoma, non-Hodgkin's; Eczema, atopic; Infection, HIV/AIDS; Rhinitis, allergic, general
						All drugs
						APN-401; APN-4
						ABN-912; Bindarit; Carlum
						AZD-4818; BMS-817399; CCX-354; MIP-1alpha, Wyeth; NOX-E36; PS-0312
						AGI-1096; AZ-889; AZD-2423; AZD-5069; AZD-6942; CCL2 antagonists, Telik; CCR2 antagonist, OraPharma; CCR2b antagonist, CBT; CCX-140; EPX-102216; NIBR-6465; PF-4136309; TEI-8535; Cenicrivir
						766994; ASM-8; AZD-1744; QAP-6
						CCR4-ZFN, T-cell, Sangamo; GSK-2239633; K-327; RS-1269; RS-1748; Mogamulizum

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
CCR5	chemokine (C-C motif) receptor 5	Celiac disease	65	rs13098911-A (0.10)	Celiac disease	Alzheimer's disease; Amyotrophic lateral sclerosis; Arthritis, rheumatoid; Cachexia; Cancer, general; Cancer, lymphoma, non-Hodgkin's; Colitis, ulcerative; Cushing's disease; Diabetes, Type 2; Herpetic keratitis; Infection, HIV prophylaxis; Infection, HIV/AIDS; Infection, hepatitis-A virus; Infection, hepatitis-B virus; Infection, hepatitis-C virus; Infection, human papilloma virus, unspecified; Infection, human sclerositis, general; Psoriasis
CCR9	chemokine (C-C motif) receptor 9	Celiac disease	65	rs13098911-A (0.10)	Celiac disease	Coeliac disease; Colitis, ulcerative; Crohn's disease; Inflammatory bowel disease, general
CD19	CD19 molecule	Crohn's disease	83	rs151181-G (0.39)	Crohn's disease	Arthritis, rheumatoid; Cancer, haematological, general; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, general; Cancer, lymphoma, B-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Scleroderma
CD28	CD28 molecule	Celiac disease	65	rs4675374-A (0.22)	Celiac disease	Cancer, breast; Cancer, colorectal; Cancer, haematological, general; Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, prostate; Cancer, sarcoma, general; Cancer, solid, general; Psoriasis; Transplant rejection, general
CD33	CD33 molecule	Alzheimer's disease	28	rs3826656-? (NR), rs3865444-? (0.70)	Alzheimer's disease	Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, lung, small cell; Myelodysplastic syndrome
CD36	CD36 molecule (thrombospondin receptor)	Left ventricular mass	3	rs10499859-? (0.45)	Left ventricular mass	Cancer, brain; Cancer, solid, general; Polycystic ovarian syndrome
						All drugs
						53926; AOP-RANTES; AZD-5672; CCR5 antagonists, GlaxoSmithKline-2; CCR5 antagonists, Ono; CCR5mAb004; ESN-196; INCB-15050; NIBR-6465; PF-232798; PRO-140; RAP-101; RAP-160; RNAi HIV therapy, stem cell, Benitec; RPI-MN; SB-728; SMA CCR-5/CXCR-4; SP-01A; TAK-220; VCH-286; Ancriviroc; Aplaviroc hydrochloride; Cenicriviroc; Dapivirine + maraviroc, IPM; Maraviroc; Nifediviroc; Reticulose, ADVIR; Vicriviroc malea
						CCX-2
						AFM-11; AFM-12; GBR-401; MDX-1342; MEDI-551; Oncolysin B; SAR-3419; SGN-19A; XmAb-5574; Blinatumom
						AlloStim; Antisense 16064; CD40 inhibitors, Solvay; PRO-15
						AML therapy, Micromet; HuM195-Ac-225; IMG-633; Gemtuzumab ozogamicin; Lintuzum
						ABT-898; PF-48568

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
CD6	CD6 molecule	Multiple sclerosis	59	rs17824933-G (0.25), rs4939490-? (NR)	Multiple sclerosis	Arthritis, rheumatoid; Cancer, lymphoma, non-Hodgkin's; Psoriasis	Anti-CD6 MAb, Bioc	
CD80	CD80 molecule	Celiac disease	65	rs11712165-C (0.39)	Celiac disease	Ankylosing spondylitis; Arthritis, juvenile; Arthritis, psoriatic; Arthritis, rheumatoid; Asthma; Cancer, bladder; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, non-Hodgkin's; Cancer, prostate; Colitis, ulcerative; Crohn's disease; Lupus nephritis; Psoriasis; Transplant rejection, bone marrow; Transplant rejection, general	ASP-2408; Prostavac; RhuDex; Abatacept; BioXpress; Anti-B7 MAb, Solvay; Anti-B7 MABs, Wyeth; Fowlpox-TRICOM; Galixim	
CD80	CD80 molecule	Primary biliary cirrhosis	26	rs2293370-G (0.80)	Primary biliary cirrhosis	Ankylosing spondylitis; Arthritis, juvenile; Arthritis, psoriatic; Arthritis, rheumatoid; Asthma; Cancer, bladder; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, non-Hodgkin's; Cancer, prostate; Colitis, ulcerative; Crohn's disease; Lupus nephritis; Psoriasis; Transplant rejection, bone marrow; Transplant rejection, general	ASP-2408; Prostavac; RhuDex; Abatacept; BioXpress; Anti-B7 MAb, Solvay; Anti-B7 MABs, Wyeth; Fowlpox-TRICOM; Galixim	
CDK2	cyclin-dependent kinase 2	Type 1 diabetes	50	rs1701704-C (0.35)	Type 1 diabetes	Cancer, adrenal; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, nasopharyngeal; Cancer, neuroendocrine, general; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general; Cancer, thymoma; Glaucoma; Glomerulonephritis; Myelodysplastic syndrome	AT-7519; CGP-60474; CGP-74514; CYC-065; PHA-848125AC; SB-1317; Alvociclib; Dinaciclib; Seliciclib; Seliciclib, Alc	

Table 1		Strongest			New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)						
CDK4	cyclin-dependent kinase 4	Celiac disease and Rheumatoid arthritis	14	rs10876993-? (NR)	Celiac disease and Rheumatoid arthritis		Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, general; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general; Cancer, squamous cell; Cancer, thymoma		AT-7519; CDK4 gene, Celera; LEE-011; LY-2835219; P-1446-05; P-276-00; PD-0332991; PHA-848125AC; Alvocid	
CDK6	cyclin-dependent kinase 6	Rheumatoid arthritis	49	rs42041-G (0.24)	Rheumatoid arthritis		Cancer, breast; Cancer, gastrointestinal, stomach; Cancer, general; Cancer, head and neck; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general		LEE-011; LY-2835219; PD-0332991; Alvocid	
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Glioma	7	rs2157719-? (NR), rs4977756-G (0.60)	Glioma		Cancer, general		CYC1	
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Melanoma	4	rs7023329-A (0.50)	Melanoma		Cancer, general		CYC1	

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Intracranial aneurysm	8		rs1333040-T (0.55), rs1333040-T (0.56)	Intracranial aneurysm	Cancer, general	CYC1
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Abdominal aortic aneurysm	2		rs2383207-G (0.49)	Abdominal aortic aneurysm	Cancer, general	CYC1
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Myocardial infarction	14		rs10757278-G (0.45), rs4977574-G (0.56)	Myocardial infarction	Cancer, general	CYC1
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Type 2 diabetes	61		rs10811661-T (0.83), rs10811661-T (0.85), rs10965250-G (NR), rs1333051-A (NR), rs2383208-A (0.55), rs564398-T (0.56), rs7020996-C (NR)	Type 2 diabetes	Cancer, general	CYC1
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Breast cancer	37		rs1011970-T (0.17)	Breast cancer	Cancer, general	CYC1

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	Coronary heart disease	78	2-SNP haplotype-4 ((GG)), rs1333049-C (0.47), rs4977574-G (0.46)	Coronary heart disease	Cancer, general
CETP	cholesteryl ester transfer protein, plasma	Age-related macular degeneration	16	rs3764261-A (0.32), rs3764261-A (0.33)	Age-related macular degeneration	Atherosclerosis; Hypercholesterolaemia; Hyperlipidaemia, general; Obesity
CETP	cholesteryl ester transfer protein, plasma	HDL Cholesterol - Triglycerides	6	rs173539-C (NR)	HDL Cholesterol - Triglycerides	Atherosclerosis; Hypercholesterolaemia; Hyperlipidaemia, general; Obesity
CETP	cholesteryl ester transfer protein, plasma	Coronary heart disease	78	rs16965039-T (0.94)	Coronary heart disease	Atherosclerosis; Hypercholesterolaemia; Hyperlipidaemia, general; Obesity
						56419; ATH-03; CETP inhibitor, Johnson & Johnson; CETP inhibitors, Bayer-2; CETP inhibitors, Merck & Co; CETP vaccine, Celldex; CP-800569; DRL-17822; FM-VP4; JTT-302; PF-3185043; Pharmaprojects No. 5691; Ro-51-32822; TA-8995; Anacetrapib; Atorvastatin + torcetrapib; Dalcetrapib; Dalcetrapib + atorvastatin, Roche; Evacetrapib; Torcetrap
						56419; ATH-03; CETP inhibitor, Johnson & Johnson; CETP inhibitors, Bayer-2; CETP inhibitors, Merck & Co; CETP vaccine, Celldex; CP-800569; DRL-17822; FM-VP4; JTT-302; PF-3185043; Pharmaprojects No. 5691; Ro-51-32822; TA-8995; Anacetrapib; Atorvastatin + torcetrapib; Dalcetrapib; Dalcetrapib + atorvastatin, Roche; Evacetrapib; Torcetrap
						56419; ATH-03; CETP inhibitor, Johnson & Johnson; CETP inhibitors, Bayer-2; CETP inhibitors, Merck & Co; CETP vaccine, Celldex; CP-800569; DRL-17822; FM-VP4; JTT-302; PF-3185043; Pharmaprojects No. 5691; Ro-51-32822; TA-8995; Anacetrapib; Atorvastatin + torcetrapib; Dalcetrapib; Dalcetrapib + atorvastatin, Roche; Evacetrapib; Torcetrap

Table 1

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
CFH	complement factor H	Age-related macular degeneration	16	rs1061170-? (NR), rs1061170-C (0.37), rs10737680-A (0.566), rs1329424-T (0.351), rs1329428-? (NR), rs1410996-? (NR), rs380390-C (0.70 (HapMap CEU))	Age-related macular degeneration	Haemolytic uraemic syndrome
CFH	complement factor H	Nephropathy	23	rs6677604-? (0.77 (EA))	Nephropathy	Haemolytic uraemic syndrome
CFH	complement factor H	Meningococcal disease	2	rs426736-? (0.84)	Meningococcal disease	Haemolytic uraemic syndrome
CHEK2	CHK2 checkpoint homolog (S. pombe)	Esophageal cancer and gastric cancer	4	rs738722-T (0.25)	Esophageal cancer and gastric cancer	Cancer, bladder; Cancer, leukaemia, chronic lymphocytic; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, mesothelioma; Cancer, neuroendocrine, general; Cancer, oral; Cancer, ovarian; Cancer, solid, general
						Complement Factor H, L
						Complement Factor H, L
						Complement Factor H, L
						Complement Factor H, L

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
CHRM3	cholinergic receptor, muscarinic 3	Hypertension	22		rs2820037-T (0.14)	Hypertension	Alzheimer's disease; Asthma; Benign prostatic hyperplasia; Bronchitis, chronic; Cancer, colorectal; Cancer, lung, small cell; Cancer, prostate; Cholangitis, unspecified; Cholecystitis, unspecified; Cholelithiasis; Chronic obstructive pulmonary disease; Colitis, general; Cystic fibrosis; Depression, bipolar; Diabetes, Type 2; Dyskinesia, biliary; Enuresis; Epilepsy, general; Gastritis; Gastro-oesophageal reflux; Glaucoma; Hypersalivation; Incontinence, urinary; Inflammation, urinary tract; Irritable bowel syndrome; Ischaemia, cerebral; Keratoconjunctivitis; Muscle spasm, general; Nausea and vomiting, general; Neurogenic bladder; Oesophagitis, reflux; Overactive bladder; Pain, musculoskeletal, general; Pain, neuropathic; Pancreatitis; Pollakisuria; Postcholecystectomy syndrome; Psychosis, bipolar; Psychosis, general; Radio/chemotherapy-induced injury, general; Schizophrenia; Ulcer, GI, general; Ulcer, duodenal; Ulcer, gastric; Xerophthalmia; Xerostomia	55284; 62380; ANAVEX-1007; ANAVEX-19-144; ANAVEX-2-73; ANAVEX-7-1037; GSK-961081; J-104135; J-115311; LAS-190792; PSD-506; PT-010; Pilopex; SVT-47060; TRN-157; Acridinium bromide; Acridinium bromide + ICS; Acridinium bromide + formoterol; Alvameline; Atropine+pralidoxime chloride; Cimetropium bromide; Clonidine + oxybutynin; Darifenacin hydrobromide; Darotropium bromide; Denaverine hydrochloride; Formoterol fumarate + glycopyrrolate, Pearl; Gabapentin+oxybutynin, Dynogen; Glycopyrrolate + indacaterol, Sosei; Glycopyrrolate, Chiesi; Glycopyrrolate, Pearl; Glycopyrrolate, Shionogi; Glycopyrrolate, Sosei; Hyoscymamine sulfate; Hyoscymamine sulfate, InKine; Hyoscymamine sulfate, OraQuick; Imidafenacin; Imidafenacin, Kyorin (orally disintegrating); Ipratropium, Boehringer; Levalbuterol + ipratropium; Mebeverine + ispaghula; Olanzapine + pamoate acid; Olanzapine + zonisamide, Or; Olanzapine, Alkermes; Olanzapine, RAIM; Olanzapine, Zydus; Olodaterol + tiotropium bromide; Oxybutynin gel, Antares; Oxybutynin ring, Barr; Oxybutynin, Alza; Oxybutynin, Auxilium; Oxybutynin, FemmePharma; Oxybutynin, Labopharm; Oxybutynin, Phoenix; Oxybutynin, THERx; Oxybutynin, TheraTech; Oxybutynin, gel, Watson; Pilocarpine + tolterodine, TheraVida; Pilocarpine, Cytokine; Pilocarpine, InSite; Pilocarpine, MGI; Pilocarpine, Pharmos; Propiverine hydrochloride; Salbutamol+ipratropium bromide; Scopolamine, Alza; Scopolamine, ETT; Secoverine;

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes					
CHRM3 continued	cholinergic receptor, muscarinic 3	Hypertension	22		rs2820037-T (0.14)	Hypertension	Alzheimer's disease; Asthma; Benign prostatic hyperplasia; Bronchitis, chronic; Cancer, colorectal; Cancer, lung, small cell; Cancer, prostate; Cholangitis, unspecified; Cholelithiasis; Cholecystitis, unspecified; Chronic obstructive pulmonary disease; Colitis, general; Cystic fibrosis; Depression, bipolar; Diabetes, Type 2; Dyskinesia, biliary; Enuresis; Epilepsy, general; Gastritis; Gastro-oesophageal reflux; Glaucoma; Hypersalivation; Incontinence, urinary; Inflammation, urinary tract; Irritable bowel syndrome; Ischaemia, cerebral; Keratoconjunctivitis; Muscle spasm, general; Nausea and vomiting, general; Neurogenic bladder; Oesophagitis, reflux; Overactive bladder; Pain, musculoskeletal, general; Pain, neuropathic; Pancreatitis; Pollakisuria; Postcholecystectomy syndrome; Psychosis, bipolar; Psychosis, general; Radio/chemotherapy-induced injury, general; Schizophrenia; Ulcer, GI, general; Ulcer, duodenal; Ulcer, gastric; Xerophthalmia; Xerostomia	Solifenacin; Solifenacin succinate; Solifenacin succinate + tamsulosin hydrochloride OCAS; Solifenacin succinate, ODT; Tamsulosin + tolterodine; Tarafenacin; Tiemonium metilsulfate; Tiemonium, Formenti; Tiotropium bromide; Tiotropium bromide + formoterol fumarate + ciclesonide, Cipla; Tolterodine; Tolterodine, extended-release; TrepiButone; Trimebutine maleate + mosapride citrate, Samil; Trimebutine, Labopharm; Vamicami
CHRNA3	cholinergic receptor, nicotinic, alpha 3	Chronic obstructive pulmonary disease	7		rs13180-? (0.36), rs8034191-C (0.33)	Chronic obstructive pulmonary disease	Addiction, alcohol; Addiction, nicotine	CP-6019
CHRNA3	cholinergic receptor, nicotinic, alpha 3	Lung cancer	12		rs8034191-? (NR), rs8034191-C (0.34), rs8034191-G (NR)	Lung cancer	Addiction, alcohol; Addiction, nicotine	CP-6019
CHRNA3	cholinergic receptor, nicotinic, alpha 3	Lung adenocarcinoma	8		rs1051730-T (0.35)	Lung adenocarcinoma	Addiction, alcohol; Addiction, nicotine	CP-6019

Table 1					Strongest					
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs			
CHRNA4	cholinergic receptor, nicotinic, alpha 4	Chronic obstructive pulmonary disease	7	rs8034191-C (0.33)	Chronic obstructive pulmonary disease	Addiction, nicotine; Alzheimer's disease; Attention deficit hyperactivity disorder; Cognitive disorder, unspecified; Dementia, senile, general; Depression, general; Depression, major depressive disorder; Irritable bowel syndrome; Neuropathy, diabetic; Pain, general; Pain, neuropathic; Pain, post-herpetic; Pain, post-operative; Schizophrenia	ABT-560; AZD-1446; CP-601927; NS-9283; S-(+)-mecamylamine HCl, Targacept; SUVN-90121; SUVN-911; TC-2696; TC-6499; Dianicline; Dianicline + rimonabant; Ispronicline; Sofinicine; Tebanicline tosylate; Varenicline tartrate; Varenicline tartrate, T			
CHRN4	cholinergic receptor, nicotinic, beta 4	Lung cancer	12	rs8034191-C (0.34), rs8034191-G (NR)	Lung cancer	Addiction, alcohol; Addiction, nicotine	CP-6019			
CLU	clusterin	Panic disorder	10	rs17466684-? (0.09)	Panic disorder	Cancer, bladder; Cancer, breast; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Cancer, renal	AB-1685; Custirs			
CLU	clusterin	Alzheimer's disease	28	3-SNP haplotype (0.26), rs11136000-? (0.60), rs1532278-? (0.64), rs569214-? (NR)	Alzheimer's disease	Cancer, bladder; Cancer, breast; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Cancer, renal	AB-1685; Custirs			
COL1A1	collagen, type I, alpha 1	Breast cancer	37	rs2075555-? (NR)	Breast cancer	Cancer, general; Macular degeneration, age-related, general	D			
COL4A1	collagen, type IV, alpha 1	Arterial stiffness	1	rs3742207-C (0.44)	Arterial stiffness	Cancer, general; Macular degeneration, age-related, general	D			
COL4A1	collagen, type IV, alpha 1	Coronary heart disease	78	rs4773144-G (0.44)	Coronary heart disease	Cancer, general; Macular degeneration, age-related, general	D			
CPS1	carbamoyl-phosphate synthase 1, mitochondrial	Chronic kidney disease	67	rs7422339-A (0.32)	Chronic kidney disease	Hyperammonaemia	Carglumic acid, Orphan Euro			

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes					
CR1	complement component (3b/4b) receptor 1 (Knops blood group)	Alzheimer's disease	28		2-SNP haplotype (0.18), rs3818361-? (0.19), rs6701713-A (0.20)	Alzheimer's disease	Infection, <i>Candida albicans</i> ; Infection, anthrax; Infection, anthrax prophylaxis; Infection, staphylococcal; Ischaemia, cerebral; Macular degeneration, age-related, general; Renal failure; Reperfusion injury; Respiratory distress syndrome, adult; Surgery adjunct; Transplant rejection, general	CDX-1135; Candida HP; ETI-204; ETI-211; TP
CRHR1	corticotropin releasing hormone receptor 1	Bone mineral density	42		rs9303521-T (0.46)	Bone mineral density	Anxiety, general; Arthritis, rheumatoid; Asthma; Cancer, brain; Depression, general; Depression, major depressive disorder; Diagnosis, general; Epilepsy, general; Head trauma; Inflammation, ocular; Insomnia; Irritable bowel syndrome; Ischaemia, cerebral; Oedema, cerebral; Post-traumatic stress disorder; Social anxiety disorder	586529; AAG-561; E-2508; MCI-028; NBI-27155; NBI- 30545; NBI-30775; NBI-34041; NBI-35965; ONO- 2333Ms; Pharmaprojects No. 5142; SSR-125543A; Corticoreslin acetate; Pivagabine; Verucerfo
CRP	C-reactive protein, pentraxin-related	Lung cancer	12		rs2808630-G (NR)	Lung cancer	Arthritis, rheumatoid; Atherosclerosis; Cancer, myeloma; Fibrillation, atrial; Renal failure; Respiratory distress syndrome, adult; Respiratory distress syndrome, infant; Transplant rejection, bone marrow	ISIS-353512; Pharmaprojects No. 51
CSF1	colony stimulating factor 1 (macrophage)	Paget's disease	9		rs10494112-G (0.20), rs484959-? (0.51)	Paget's disease	Arthritis, rheumatoid; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate	ARRY-382; PD 03603

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
CSF2RA	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	Schizophrenia	33	rs4129148-C (NR)	Schizophrenia	Anaemia, aplastic; Anaemia, radio/chemotherapy-induced; Anaemia, renal disease-induced; Arthritis, rheumatoid; Asthma; Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, renal; Cancer, sarcoma, Kaposi's; Cancer, skin, general; Crohn's disease; Granulocytopenia; Infection, Escherichia coli prophylaxis; Infection, HIV/AIDS; Infection, unspecified; Neutropenia, general; Poisoning, radiation; Radio/chemotherapy-induced infection; Radio/chemotherapy-induced injury, bone marrow, general; Radio/chemotherapy-induced injury, bone marrow, neutropenia; Radio/chemotherapy-induced injury, general; Sepsis; Stem cell mobilization; Thrombocytopenic purpura; Ulcer, diabetic; Ulcer, venostasis; Vaccine adjunct; Wound healing
CTLA4	cytotoxic T-lymphocyte-associated protein 4	Type 1 diabetes	50	rs3087243-? (NR), rs3087243-A (NR)	Type 1 diabetes	Arthritis, rheumatoid; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, genitourinary; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Infection, HIV/AIDS; Infection, hepatitis-C virus; Myelodysplastic syndrome; Transplant rejection, general
						All drugs BBT-007; CSF-GM, Cangene; CSF-GM, LGLS; KB-002; KB-003; MEN-11300; Mavrilimumab; Molgramostim; Molgramostim, Amoytop; Molgramostim, Probiomed; Molgramostim, Zenotech; Sargramostim; Talactoferrin al
						ASP-2408; Belatacept; Ipilimumab; Tremelimum

Table 1		Strongest			New suggested			Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	Indication	Indication	Indication	Indication	Indication	Indication	Indication
CTLA4	cytotoxic T-lymphocyte-associated protein 4	Celiac disease	65	rs4675374-A (0.22)	Celiac disease	Celiac disease	Celiac disease	Arthritis, rheumatoid; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, genitourinary; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Infection, HIV/AIDS; Infection, hepatitis-C virus; Myelodysplastic syndrome; Transplant rejection, general	Arthritis, rheumatoid; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, genitourinary; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Infection, HIV/AIDS; Infection, hepatitis-C virus; Myelodysplastic syndrome; Transplant rejection, general	ASP-2408; Belatacept; Ipilimumab; Tremelimum	ASP-2408; Belatacept; Ipilimumab; Tremelimum
CTLA4	cytotoxic T-lymphocyte-associated protein 4	Alopecia areata	11	rs1024161-A (0.40)	Alopecia areata	Alopecia areata	Alopecia areata	Arthritis, rheumatoid; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, genitourinary; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Infection, HIV/AIDS; Infection, hepatitis-C virus; Myelodysplastic syndrome; Transplant rejection, general	Arthritis, rheumatoid; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, genitourinary; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Infection, HIV/AIDS; Infection, hepatitis-C virus; Myelodysplastic syndrome; Transplant rejection, general	ASP-2408; Belatacept; Ipilimumab; Tremelimum	ASP-2408; Belatacept; Ipilimumab; Tremelimum
CTNNA1	catenin (cadherin-associated protein), beta 1, 88kDa	Bone mineral density	42	rs87938-A (0.45)	Bone mineral density	Bone mineral density	Bone mineral density	Adenoma, colorectal; Cancer, colorectal; Cancer, pancreatic; Cancer, solid, general	Adenoma, colorectal; Cancer, colorectal; Cancer, pancreatic; Cancer, solid, general	CEQ-508; PRI-7	CEQ-508; PRI-7
CTSH	cathepsin H	Type 1 diabetes	50	rs3825932-? (NR), rs3825932-T (0.68)	Type 1 diabetes	Type 1 diabetes	Type 1 diabetes	Dystrophy, Duchenne's muscular	Dystrophy, Duchenne's muscular	Loxistat	Loxistat
CUBN	cubilin (intrinsic factor-cobalamin receptor)	Urinary albumin excretion	3	rs1801239-T (0.90)	Urinary albumin excretion	Urinary albumin excretion	Urinary albumin excretion	Amyotrophic lateral sclerosis; Anaemia, pernicious; Anaemia, unspecified; Neuropathy, diabetic; Neuropathy, unspecified; Nutrition	Amyotrophic lateral sclerosis; Anaemia, pernicious; Anaemia, unspecified; Neuropathy, diabetic; Neuropathy, unspecified; Nutrition	Mecobalamin, Eisai; Vitamin B12, MDR	Mecobalamin, Eisai; Vitamin B12, MDR

Table 1					Strongest					
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs			
CXCL12	chemokine (C-X-C motif) ligand 12	Myocardial infarction	14	rs1746048-C (0.84)	Myocardial infarction	Cancer, haematological, general; Cancer, solid, general; Macular degeneration, age-related, general; Retinopathy, diabetic; Stem cell mobilization	NOX-A			
CXCL12	chemokine (C-X-C motif) ligand 12	Coronary heart disease	78	rs1746048-C (0.87), rs501120-T (0.87)	Coronary heart disease	Cancer, haematological, general; Cancer, solid, general; Macular degeneration, age-related, general; Retinopathy, diabetic; Stem cell mobilization	NOX-A			
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Parkinson's disease	47	rs17115100-G (0.91)	Parkinson's disease	Cancer, breast; Cancer, prostate	ANG-3407; YM-116; Abiraterone acetate; Biphenylmethylimidazole derivatives, Takeda; . Galeterone; Orteron			
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Coronary heart disease	78	rs12413409-G (0.89)	Coronary heart disease	Cancer, breast; Cancer, prostate	ANG-3407; YM-116; Abiraterone acetate; Biphenylmethylimidazole derivatives, Takeda; Galeterone; Orteron			
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Coffee consumption	3	rs2472297-T (0.265)	Coffee consumption	Cancer, solid, general	SF-DF-2			
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Diastolic blood pressure	24	rs1378942-C (0.36)	Diastolic blood pressure	Cancer, solid, general	SF-DF-2			
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Multiple sclerosis	59	rs703842-A (0.67)	Multiple sclerosis	Hyperthyroidism	CTA-1			
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Osteonecrosis of the jaw	1	rs1934951-T (0.12)	Osteonecrosis of the jaw	Hypercholesterolaemia; Hyperlipidaemia, general	Gemfibroz			
DCPS	decapping enzyme, scavenger	Longevity	23	rs1695739-G (0.04)	Longevity	Muscular atrophy, spinal	RG-30			

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	Acute lymphoblastic leukemia	13	rs11978267-G (0.27)	Acute lymphoblastic leukemia	Parkinson's disease
DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	Malaria	3	rs1451375-? (0.78)	Malaria	Parkinson's disease
DHODH	dihydroorotate dehydrogenase	Attention deficit hyperactivity disorder and conduct disorder	30	rs16973500-C (0.86)	Attention deficit hyperactivity disorder and conduct disorder	Arthritis, juvenile; Arthritis, psoriatic; Arthritis, rheumatoid; Colitis, ulcerative; Crohn's disease; Infection, HIV/AIDS; Infection, malaria; Multiple sclerosis, general; Transplant rejection, general
DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	HIV-1 replication	1	rs12483205-? (NR)	HIV-1 replication	Down's syndrome
DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Metabolic syndrome	24	rs2835810-? (0.37)	Metabolic syndrome	Down's syndrome
					All drugs	
					AV-201; ProSavin; XP-21279 + carbidopa; Carbidopa + levodopa CR, IMPAX; Carbidopa + levodopa ER, Depomed; Carbidopa + levodopa GR, Intec; Carbidopa + levodopa, IMPAX; Carbidopa + levodopa, Penwest; Carbidopa + levodopa, UCB; Carbidopa+entacapone+levodopa, Orion Pharma-2; Carbidopa+levodopa-1, Nouvel; Carbidopa, NeuroDerm; Entacapone+levodopa+carbidopa; Etilevodopa; Levodopa + benserazide, GEOMAT; Levodopa, Orion Pharma; Melevodopa; Melevodopa + carbidopa,	
					AV-201; ProSavin; XP-21279 + carbidopa; Carbidopa + levodopa CR, IMPAX; Carbidopa + levodopa ER, Depomed; Carbidopa + levodopa GR, Intec; Carbidopa + levodopa, IMPAX; Carbidopa + levodopa, Penwest; Carbidopa + levodopa, UCB; Carbidopa+entacapone+levodopa, Orion Pharma-2; Carbidopa+levodopa-1, Nouvel; Carbidopa, NeuroDerm; Entacapone+levodopa+carbidopa; Etilevodopa; Levodopa + benserazide, GEOMAT; Levodopa, Orion Pharma; Melevodopa; Melevodopa + carbidopa,	
					4SC-302; FK-778; Genz-667348; LAS-186323; LAS-187247; Leflunomide; Vidofludim	
					DYRK1A inhibitors, NeuroNasce	
					DYRK1A inhibitors, NeuroNasce	

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication			Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes								
ENG	endoglin	Metabolic syndrome	24	rs7865146-A (0.37)	Metabolic syndrome			Cancer, breast; Cancer, fallopian tube; Cancer, ovarian; Cancer, peritoneal; Cancer, prostate; Cancer, solid, general; Macular degeneration, age-related, general		TRC-1	
ENPEP	glutamyl aminopeptidase (aminopeptidase A)	Atrial fibrillation/atrial flutter	2	rs10033464-T (0.08), rs2200733-T (0.11)	Atrial fibrillation/atrial flutter			Hypertension, general		QGC-0	
EPHA1	EPH receptor A1	Alzheimer's disease	28	rs11767557-? (0.81)	Alzheimer's disease			Cancer, colorectal; Cancer, fallopian tube; Cancer, haematological, general; Cancer, leukaemia, acute myelogenous; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, peritoneal; Cancer, renal		ENMD-20	
ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Type 1 diabetes	50	rs11171739-C (0.42), rs1701704-C (0.35), rs2292239-? (NR), rs2292239-A (0.34), rs2292239-A (NR)	Type 1 diabetes			Cancer, breast; Cancer, endometrial; Cancer, fallopian tube; Cancer, general; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, peritoneal; Cancer, solid, general		AC-480; HM-781-36B; MEHD-7945A; MM-111; MM-121; RB-200h; U3-1287; RhErbB3	

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest	New suggested indication	Current indications	All drugs
				SNP-Risk Allele (frequency)			
ESR1	estrogen receptor 1	Alcohol dependence	8	rs6902771-C (0.51)	Alcohol dependence	Acne; Alzheimer's disease; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Contraceptive, female; Cushing's disease; Depression, general; Eczema, seborrhoeic; Endometriosis; Gynaecomastia; Hormone replacement therapy; Hypogonadism; Infarction, myocardial; Infection, vaginal; Infertility, male; Inflammation, vaginal; Insulin-related metabolic syndrome; Lupus erythematosus, systemic; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Obesity; Osteoporosis; Parkinson's disease; Radio/chemotherapy-induced injury, general; Seborrhoea; Sex-chromosome abnormality, Turner's syndrome; Sexual dysfunction, female; Sexual dysfunction, male; Sjogren's syndrome; Vaccine adjunct; Wound healing	11096; 17Å-estradiol, Renovo; 3339; AZD-4992; DHEA + acolbifene, Endoceutics; Diviseq; Femarelle; GTx-758; GTx-822; GW-5638; IP-1162; MK-6913; Nestorone + ethinylestradiol vaginal ring, Population Council; OTE-F, Pantarhei; P-09; RAD-1901; SERD programme, Aragon; SERM + toxin, SEEK; Synphase; TAS-108; VAL-201; Z-tamoxifen; Anti-estrogens, Olema; Antiobesity SERM, Bionovo; Arzoxifene hydrochloride; Bazedoxifene acetate; Bazedoxifene acetate+Premarin; Chlormadinone acetate + ethinyl estradiol; Contraceptive, BioSante; Cyproterone acetate + estradiol valerate, Bayer; Cyproterone acetate + ethinylestradiol, Douglas; Desogestrel + estradiol, Akzo; Desogestrel + estrogen, tri; Desogestrel+ethinylestrad (1); Desogestrel+ethinylestrad (2); Desogestrel+ethinylestrad (3); Desogestrel/ethinyl estradiol + ethinyl estradiol, Teva; Dienogest + estradiol valerate; Dienogest + estradiol valerate, sequential, Bayer Schering; Dienogest + ethinylestradiol; Droloxifene; Drospirenone + estradiol, Bayer Schering; Drospirenone + estradiol, Bayer-2; Drospirenone + ethinyl estradiol, Bayer; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-2; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-1; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-3; Drospirenone + ethinylestradiol, flexible dose, Bayer; Endoxifen; Estetrol; Estradiol (17Å), Noven; Estradiol (17Å), Solvay; Estradiol (patch), TheraTech; Estradiol + Nestorone, Antares; Estradiol + gestodene, Bayer; Estradiol + gestodene, Wyeth-2; Estradiol + levonorgestrel (patch), Bayer Schering; Estradiol + levonorgestrel, 3M; Estradiol + levonorgestrel, Jenderm;

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
ESR1 continued	estrogen receptor 1	Alcohol dependence	8	rs6902771-C (0.51)
				Alcohol dependence
				Acne; Alzheimer's disease; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Contraceptive, female; Cushing's disease; Depression, general; Eczema, seborrhoeic; Endometriosis; Gynaecomastia; Hormone replacement therapy; Hypogonadism; Infarction, myocardial; Infection, vaginal; Infertility, male; Inflammation, vaginal; Insulin-related metabolic syndrome; Lupus erythematosus, systemic; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Obesity; Osteoporosis; Parkinson's disease; Radio/chemotherapy-induced injury, general; Seborrhoea; Sex-chromosome abnormality, Turner's syndrome; Sexual dysfunction, female; Sexual dysfunction, male; Sjogren's syndrome; Vaccine adjunct; Wound healing
				New suggested indication
				Current indications
				All drugs
				Estradiol + levonorgestrel, Merck KGaA-1; Estradiol + levonorgestrel-2, Merck KGaA; Estradiol + norgestrol acetate; Estradiol + norethisterone; Estradiol + norethisterone, 4-day; Estradiol + norethisterone, Elan/Wyeth; Estradiol + norethisterone, Noven; Estradiol + norethisterone, Novo Nordisk; Estradiol + norethisterone, Pierre Fabre; Estradiol + norethisterone, Sandoz; Estradiol + progesterone, CAFET; Estradiol + progesterone, Acrux; Estradiol + trimegestone; Estradiol 4-day, Elan; Estradiol 7-day, Beta; Estradiol 7-day, Permtec; Estradiol acetate, Warner-1; Estradiol gel, Theramex; Estradiol oral, Novo Nordisk; Estradiol patch, 3M Pharmaceuticals; Estradiol transdermal, Ortho; Estradiol vaginal, Novo Nordisk; Estradiol valerate + MPA, Orion-2; Estradiol valerate + levomefolate calcium, Bayer; Estradiol valerate + medroxyprogesterone acetate, Orion; Estradiol valerate + medroxyprogesterone, Orion; Estradiol valerate + norethisterone enanthate, Bayer; Estradiol valerate, Orion; Estradiol(17Å) + norgestimate; Estradiol+dydrogesterone, Solv; Estradiol, 3M Pharmaceutical; Estradiol, 7-day patch, Rottapharm; Estradiol, Acrux; Estradiol, Alza; Estradiol, Antares; Estradiol, Bayer; Estradiol, Cilag; Estradiol, Elan; Estradiol, Endocon; Estradiol, MDRNA; Estradiol, Nitto Denko; Estradiol, Noven; Estradiol, Ortho-McNeil; Estradiol, Pharmacia; Estradiol, Pierre Fabre; Estradiol, Rottapharma; Estradiol, Servier; Estradiol, Solvay; Estradiol, Watson-2; Estradiol, pharmed; Estradiol, transdermal, Cipla; Estramustine phosphate sodium; Estriol, Adeona; Estrogen + progesterone, Agile-2; Estrogen + progestin, Cygnus; Estrogen + progesterone, Shire; Estrogen + progesterone, Alza;

Table 1					
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication
ESR1 continued	estrogen receptor 1	Alcohol dependence	8	rs6902771-C (0.51)	Alcohol dependence
					Current indications
					All drugs
					Acne; Alzheimer's disease; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Contraceptive, female; Cushing's disease; Depression, general; Eczema, seborrhoeic; Endometriosis; Gynaecomastia; Hormone replacement therapy; Hypogonadism; Infarction, myocardial; Infection, vaginal; Infertility, male; Inflammation, vaginal; Insulin-related metabolic syndrome; Lupus erythematosus, systemic; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Obesity; Osteoporosis; Parkinson's disease; Radio/chemotherapy-induced injury, general; Seborrhoea; Sex-chromosome abnormality, Turner's syndrome; Sexual dysfunction, female; Sexual dysfunction, male; Sjogren's syndrome; Vaccine adjunct; Wound healing Estrogen transdermal, 7-day, Merck KGaA; Estrogen+progestin, 7day, Cyg; Estrogen, Novavax; Estrogen, Noven; Estrogen, esterified, Solvay; Estrogens, conjugated, Barr; Ethinyl estradiol + norethindrone (low dose), Warner Chilcott-2; Ethinyl estradiol + norethindrone (low dose), Warner Chilcott-3; Ethinyl estradiol sulfate; Ethinyl estradiol, Cassenne; Ethinyl estradiol, Savient; Ethinylestradiol + TX-525, Th; Ethinylestradiol + levonorgestrel, Agile-1; Ethinylestradiol + levonorgestrel, Barr; Ethinylestradiol + levonorgestrel, Bayer; Ethinylestradiol + levonorgestrel, Bayer-2; Ethinylestradiol + levonorgestrel, Gynetics; Ethinylestradiol + levonorgestrel, Teva; Ethinylestradiol + levonorgestrel, Wyeth; Ethinylestradiol + norelgestromin; Ethinylestradiol + norethindrone, Nobelpharma; Ethinylestradiol + norethindrone, low-dose, Nobelpharma; Ethinylestradiol + norethisterone acetate, Warner; Ethinylestradiol + norethisterone, Daiichi; Ethinylestradiol + norethisterone, Ortho; Ethinylestradiol+etonogestrel; Ethinylestradiol+levonorgestrel, Sc; Fispemifene; Fulvestrant; Gestodene + ethinylestradiol, Bayer-2; Gestodene+ethinylestradiol, Ba; Icaritin; Idoxifene; Lasofoxifene; Levormeloxifene; Medroxyprogesterone + Premarin; Medroxyprogesterone, depot; Miproxifene phosphate; Norethindrone + ethinyl estradiol (low dose), Warner Chilcott-1; Norethindrone acetate + ethinyl estradiol, Warner Chilcott-1; Norethindrone acetate + ethinyl estradiol, Warner Chilcott-2; Ormeloxifene; Ospemifene; Panomifene; Promestriene; Raloxifene hydrochloride; Synth conjugated estrogens, B; Tamoxifen; Tamoxifen, Douglas; Tamoxifen, oral liquid, Savient; Tibolone; Toremifene citrate; Trilostane; ÅY-estradiol prodrug

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
ESR1	estrogen receptor 1	Chronic myeloid leukemia	9	rs4869742-T (0.77)
				New suggested indication
				Chronic myeloid leukemia
				Current indications
				Acne; Alzheimer's disease; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Contraceptive, female; Cushing's disease; Depression, general; Eczema, seborrheic; Endometriosis; Gynaecomastia; Hormone replacement therapy; Hypogonadism; Infarction, myocardial; Infection, vaginal; Infertility, male; Inflammation, vaginal; Insulin-related metabolic syndrome; Lupus erythematosus, systemic; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Obesity; Osteoporosis; Parkinson's disease; Radio/chemotherapy-induced injury, general; Seborrhoea; Sex-chromosome abnormality, Turner's syndrome; Sexual dysfunction, female; Sexual dysfunction, male; Sjogren's syndrome; Vaccine adjunct; Wound healing
				All drugs
				11096; 17ÅY-estradiol, Renovo; 3339; AZD-4992; DHEA + acolbifene, Endoceutics; Diviseq; Femarelle; GTx-758; GTx-822; GW-5638; IP-1162; MK-6913; Nestorone + ethinylestradiol vaginal ring, Population Council; OTE-F, Pantarhei; P-09; RAD-1901; SERD programme, Aragon; SERM + toxin, SEEK; Synphase; TAS-108; VAL-201; Z-tamoxifen; Anti-estrogens, Olema; Antiobesity SERM, Bionovo; Arzoxifene hydrochloride; Bazedoxifene acetate; Bazedoxifene acetate+Premarin; Chlormadinone acetate + ethinyl estradiol; Contraceptive, BioSante; Cyproterone acetate + estradiol valerate, Bayer; Cyproterone acetate + ethinylestradiol, Douglas; Desogestrel + estradiol, Akzo; Desogestrel + estrogen, tri; Desogestrel+ethinylestrad (1); Desogestrel+ethinylestrad (2); Desogestrel+ethinylestrad (3); Desogestrel/ethinyl estradiol + ethinyl estradiol, Teva; Dienogest + estradiol valerate; Dienogest + estradiol valerate, sequential, Bayer Schering; Dienogest + ethinylestradiol; Droloxifene; Drospirenone + estradiol, Bayer Schering; Drospirenone + estradiol, Bayer-2; Drospirenone + ethinyl estradiol, Bayer; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-2; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-1; Drospirenone + ethinylestradiol + levomefolate calcium, Bayer-3; Drospirenone + ethinylestradiol, flexible dose, Bayer; Endoxifen; Estetrol; Estradiol (17ÅY), Noven; Estradiol (17ÅY), Solvay; Estradiol (patch), TheraTech; Estradiol + Nestorone, Antares; Estradiol + gestodene, Bayer; Estradiol + gestodene, Wyeth-2; Estradiol + levonorgestrel (patch), Bayer Schering; Estradiol + levonorgestrel, 3M; Estradiol + levonorgestrel, Jenderm; Estradiol + levonorgestrel, Merck KGaA-1;

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
ESR1 continued	estrogen receptor 1	Chronic myeloid leukemia	9	rs4869742-T (0.77)

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
ESR1 continued	estrogen receptor 1	Chronic myeloid leukemia	9	rs4869742-T (0.77)	Chronic myeloid leukemia	Acne; Alzheimer's disease; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, prostate; Contraceptive, female; Cushing's disease; Depression, general; Eczema, seborrheic; Endometriosis; Gynaecomastia; Hormone replacement therapy; Hypogonadism; Infarction, myocardial; Infection, vaginal; Infertility, male; Inflammation, vaginal; Insulin-related metabolic syndrome; Lupus erythematosus, systemic; Macular degeneration, age-related, general; Menopausal symptoms, unspecified; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Obesity; Osteoporosis; Parkinson's disease; Radio/chemotherapy- induced injury, general; Seborrhoea; Sex- chromosome abnormality, Turner's syndrome; Sexual dysfunction, female; Sexual dysfunction, male; Sjogren's syndrome; Vaccine adjunct; Wound healing	Warner Chilcott-2; Ethinyl estradiol + norethindrone (low dose), Warner Chilcott-3; Ethinyl estradiol sulfonate; Ethinyl estradiol, Cassenne; Ethinyl estradiol, Savient; Ethinylestradiol + TX-525, Th; Ethinylestradiol + levonorgestrel, Agile-1; Ethinylestradiol + levonorgestrel, Barr; Ethinylestradiol + levonorgestrel, Bayer; Ethinylestradiol + levonorgestrel, Bayer-2; Ethinylestradiol + levonorgestrel, Gynetics; Ethinylestradiol + levonorgestrel, Teva; Ethinylestradiol + levonorgestrel, Wyeth; Ethinylestradiol + norelgestromin; Ethinylestradiol + norethindrone, Nobelpharma; Ethinylestradiol + norethindrone, low-dose, Nobelpharma; Ethinylestradiol + norethisterone acetate, Warner; Ethinylestradiol + norethisterone, Daiichi; Ethinylestradiol + norethisterone, Ortho; Ethinylestradiol+etonogestrel; Ethinylestradiol+levonorges,Sc; Fispemifene; Fulvestrant; Gestodene + ethinylestradiol, Bayer-2; Gestodene+ethinylestradiol,Ba; Icaritin; Idoxifene; Lasofoxifene; Levormeloxifene; Medroxyprogesterone + Premarin; Medroxyprogesterone, depot; Miproxifene phosphate; Norethindrone + ethinyl estradiol (low dose), Warner Chilcott-1; Norethindrone acetate + ethinyl estradiol, Warner Chilcott-1; Norethindrone acetate + ethinyl estradiol, Warner Chilcott-2; Ormeloxifene; Ospemifene; Panomifene; Promestriene; Raloxifene hydrochloride; Synth conjugated estrogens, B; Tamoxifen; Tamoxifen, Douglas; Tamoxifen, oral liquid,Savient; Tibolone; Toremifene citrate; Trilostane; ÅY-estradiol prodrug SR-16388; Diaryl ether-based ligands, Johnson & Johns	
ESRRA	estrogen-related receptor alpha	Crohn's disease	83	rs694739-A (0.63)	Crohn's disease	Cancer, brain; Cancer, colorectal; Cancer, lung, non-small cell; Cancer, myeloma; Cancer, prostate; Diabetes, general		
F11	coagulation factor XI	Response to statin therapy	75	rs13148903-G (0.25)	Response to statin therapy	Amyloidosis; Thrombosis, arterial; Thrombosis, general	Factor Xla inhibitor, LG Life; ISIS-404071; ISIS-TTR	

Table 1							Strongest SNP-Risk Allele (frequency)			New suggested indication			Current indications			All drugs		
Gene	Description	GWAS phenotype	No. of associated genes															
F12	coagulation factor XII (Hageman factor)	Chronic kidney disease	67				rs6420094-G (0.34)			Chronic kidney disease			Ischaemia, cerebral; Thrombosis, arterial			Factor XIIa inhibitor, C		
FAS	Fas (TNF receptor superfamily, member 6)	atrioventricular conduction	6				rs1937332-G (0.47)			Atrioventricular conduction			Arthritis, osteo; Arthritis, rheumatoid; Cancer, brain; Cancer, melanoma; Cancer, sarcoma, glial; Cancer, solid, general; Cancer, thyroid; Infarction, myocardial; Infection, HIV/AIDS; Reperfusion injury; Transplant rejection, bone marrow			DE-098; F45D9; Fas (delta) TM protein; MegaFasL; VB-1		
FASLG	Fas ligand (TNF superfamily, member 6)	Celiac disease	65				rs859637-A (0.49)			Celiac disease			Cancer, brain; Cancer, prostate; Infarction, myocardial; Ischaemia, cerebral; Sepsis; Transplant rejection, bone marrow			APG-101; Prostate cancer therapy, Sand		
FCGR2B	Fc fragment of IgG, low affinity IIb, receptor (CD32)	Ulcerative colitis	96				rs1801274-A (0.51)			Ulcerative colitis			Arthritis, rheumatoid; Cancer, lymphoma, general; Lupus erythematosus, systemic; Multiple sclerosis, general; Psoriasis; Thrombocytopenic purpura, idiopathic			SM-101; Anti-FcR antibody, SuppreM		
FDFT1	farnesyl-diphosphate farnesyltransferase 1	Non-alcoholic fatty liver disease histology	16				rs2645424-A (0.40)			Non-alcoholic fatty liver disease histology			Cardiomyopathy, ischaemic; Hypercholesterolaemia; Hyperlipidaemia, general; Hypertension, general			BMS-188494; YM-53601; Lapaquistat acetate; Squalene synthase inhibitors, Daiichi Sank		
FGF1	fibroblast growth factor 1 (acidic)	Cardiac hypertrophy	22				rs152528-? (NR)			Cardiac hypertrophy			Peripheral vascular disease			393		
FGF21	fibroblast growth factor 21	Retinal vascular caliber	18				rs2287921-T (0.47)			Retinal vascular caliber			Diabetes, Type 2; Obesity			AZ-21; FGF-21 mimetics, Ambrx; LP-101		
FGF4	fibroblast growth factor 4	Breast cancer	37				rs614367-T (0.15)			Breast cancer			Angina, general			Alferminogene tadenov		

Table 1					
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication
FLT1	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)	Cognitive performance	39	rs17086609-? (0.35)	Cognitive performance
					Cancer, biliary; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, general; Cancer, gastrointestinal, stomach; Cancer, gastrointestinal, stromal; Cancer, general; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Cancer, leukaemia, mast cell; Cancer, liver; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, nasopharyngeal; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, general; Cancer, neuroendocrine, pancreatic; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, leiomyo; Cancer, sarcoma, soft tissue; Cancer, sarcoma, synovial; Cancer, solid, general; Cancer, squamous cell; Cancer, thyroid; Cancer, urethral; Fibrosis, pulmonary, idiopathic; Herpetic keratitis; Idiopathic myelofibrosis; Macular degeneration, age-related, general; Macular degeneration, age-related, wet; Mastocytosis; Myelodysplastic syndrome; Oedema, macular, diabetic; Polycythaemia vera; Psoriasis; Retinopathy, diabetic
					AL-3818; Angiozyme; BMS-690514; CEP-5214; CEP-7055; KRN-633; MGCD-265; PRS-050; SSR-106462; STP-601; SU-14813; XL-999; Axitinib; Brivanib alaninate; Cediranib; Dovitinib lactate; Fruquintinib; Icrucumab; Intedanib; Lenvatinib; Linifanib; Midostaurin; Motesanib diphosphate; Pazopanib hydrochloride; Pazopanib hydrochloride (ophthalmic); Plitidepsin; Ponatinib; Sunitinib malate; Tivozanib; Vatalan

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
FOLH1	folate hydrolase (prostate-specific membrane antigen) 1	HDL cholesterol	37		rs7395662-G (0.61)	HDL cholesterol	Cancer, melanoma; Cancer, mesothelioma; Cancer, oesophageal; Cancer, prostate; Cancer, renal; Cancer, solid, general; Diagnosis, cancer	131I-MIP-1375; 99mTc-MIP-1340; 99mTc-MIP-1404; 99mTc-MIP-1405; DCVax-prostate; EC-0652; EC-1069; GVX-3322; INO-5150; MIP-1375; MIP-220; MKC-1106- PP; MLN-2704; PSMA ADC; PSMA gene vaccine, Progenics; Capromab pendetide; Prostate cancer immuno, Inovio; Prostate cancer vaccine, Cad
FOXO1	forkhead box O1	Central corneal thickness	6		rs2721051-G (NR), rs2755237-A (NR)	Central corneal thickness	Diabetes, Type 2	AS-18428
FSHR	follicle stimulating hormone receptor	Erectile dysfunction and prostate cancer treatment	23		rs2268363-? (0.18)	Erectile dysfunction and prostate cancer treatment	Contraceptive, female; Infertility, female; Infertility, male; Menopausal symptoms, unspecified; Osteoporosis; Polycystic ovarian syndrome	62203; ADX-68692; FSH + LH, Ferring; FSH patch, Pantec; FSH, 2nd-generation, Glycotope; FSH, LGLS; FSH, recombinant, Watson/Itero; JR-041; LAPS-FSH; Corifollitropin alfa; Follistatin, Arcarios; Follitropin alfa, BioGeneriX; Follitropin alfa, Finox; Follitropin alfa, Merck Serono; Follitropin, Dong-A; Gonadotrophin, Merck Serono; Hyperglycosylated FSH, Merck Se; Lutropin alfa+follitropin alfa; RecFSH, Organon; Urofollitropin; Urofollitropin, Ferring; Urofollitropin, Merck Serono-2; Urofollitropin, Organ
GABBR1	gamma- aminobutyric acid (GABA) B receptor, 1	Nasopharyng eal carcinoma	9		rs29232-A (0.46)	Nasopharyngeal carcinoma	Addiction, alcohol; Anxiety, general; Autism; Cerebral palsy; Depression, general; Diabetic complication, general; Dyspepsia, non-ulcer; Epilepsy, general; Gastro-oesophageal reflux; Gastroparesis; Multiple sclerosis, general; Muscle spasm; Muscle spasm, general; Pain, musculoskeletal, arthritis; Pain, neuropathic; Radio/chemotherapy-induced nausea and vomiting; Sex-chromosome abnormality, fragile X syndrome; Spasticity; Spinal cord injury	ADX-71943; ALKS-29; AVE-1876; GABA-B receptor agonists, Medisyn; Pharmaprojects No. 5525; SUN-09; Aprazolam extended-release; Arbaclofen placarbil; Arbaclofen, AGI Therapeutics; Arbaclofen, Seaside Therapeutics; Baclofen GR, Intec; Baclofen, IMPAX Laboratories; Baclofen, Sun Pharma; Baclofen, intrathecal, Medtronic; Lesogaber
GABRB3	gamma- aminobutyric acid (GABA) A receptor, beta 3	Cognitive performance	39		rs8043440-? (0.17)	Cognitive performance	Anxiety, general	XY-1029; XY-24
GALC	galactosylcerami dase	Crohn's disease	83		rs8005161-T (0.12)	Crohn's disease	Leukodystrophy, globoid cell	Galactosylceramidase, Shire; Galactosylceramidase, Zymen

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
GCK	glucokinase (hexokinase 4)	Fasting plasma glucose	6	rs4607517-A (0.18)	Fasting plasma glucose	Benign prostatic hyperplasia; Diabetes, Type 1; Diabetes, Type 2; Diabetes, general; Obesity
GDNF	glial cell derived neurotrophic factor	Major depressive disorder	34	rs270545-G (0.69)	Major depressive disorder	Amyotrophic lateral sclerosis; Parkinson's disease
GHR	growth hormone receptor	Systemic lupus erythematosus	42	rs979233-T (0.46)	Systemic lupus erythematosus	Acromegaly; Bone fracture healing; Cachexia; Crohn's disease; Dwarfism; Dysplasia, ectodermal; Growth hormone deficiency; Infertility, female; Infertility, male; Lipodystrophy; Noonan syndrome; Prader-Willi Syndrome; Renal failure; Sex-chromosome abnormality, Turner's syndrome; Short-bowel syndrome
GIP	gastric inhibitory polypeptide	Coronary heart disease	78	rs46522-T (0.53)	Coronary heart disease	Diabetes, Type 1
						All drugs
						53931; ARRY-403; AZD-1656; AZD-5658; AZD-6370; AZD-6714; GKM-001; LY-2608204; MK-0599; PFE-GKA-2; PSN-010; RO-0281675; TAK-329; TTP-399; ZYGK-1; Glucokinase activator, Banyu; Glucokinase activator, Banyu - 1; Glucokinase activator, Bristol-Myers Squibb; Glucokinase activator, LG Life Sciences; Glucokinase activator, Sanwa; Glucokinase activators, Novartis; Glucokinase activators, YuHan; Lonidamine, Thresho
						AMT-090; ANG-2008; GDNF gene therapy, Copernicus; Antiparkinsonian, Sanga
						ARX-201; CP-016; CP-024; IGF-1 + growth hormone, Ipsen; PEG-GH, PharmaEssentia; PEG-hGH, Phage Pharmaceuticals; YPEG-somatropin, Amoytop Biotech; Growth hormone, Bolder-2; Growth hormone, DelSite; Human growth hormone, Daewoong; Human growth hormone, Delpor; Human growth hormone, PDA modi; Human growth hormone, Phage Pharmaceuticals; Human growth hormone, Versartis; Pegvisomant; Somatotropin, Genentech; Somatrem, Dong-A; Somatrem, Genentech; Somatropin mimetics, Celera; Somatropin prodrug, pegylated, Ascendis; Somatropin, Access; Somatropin, Amoytop Biotech; Somatropin, Bio Sidus-1; Somatropin, Dong-A; Somatropin, HanAll; Somatropin, LG Life Sciences; Somatropin, Lilly; Somatropin, Medusa, Flamel; Somatropin, Merck Serono; Somatropin, Novo Nordisk; Somatropin, OctoDEX; Somatropin, Pfizer; Somatropin, Pfizer, pegylated; Somatropin, Prolease; Somatropin, ProLor Biotech; Somatropin, SR, LG; Somatropin, Sandoz; Somatropin, Sanofi-Synthelabo; Somatropin, Savient; Somatropin, Soligenix; Somatropin, conjugate, Hanmi; Somatropin, pegylated long-acting, Novo Nordisk; Somatropin, Antares, needle-fr
						EG-

Table 1		Strongest						
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs	
GLG1	golgi glycoprotein 1	Breast cancer	37	3-SNP haplotype 1 (0.34)	Breast cancer	Cancer, pancreatic	PAT-P	
GPR39	G protein-coupled receptor 39	Hypertension	22	2-SNP haplotype-2 ((AA))	Hypertension	Diabetes, Type 2; Obesity	Antiobesity/antidiabetic, Anchor Therapeuti	
GRIK1	glutamate receptor, ionotropic, kainate 1	Breast cancer	37	rs458685-? (NR)	Breast cancer	Neuropathy, diabetic; Pain, general; Pain, musculoskeletal, arthritis; Pain, neuropathic	LY-5456	
GRIK1	glutamate receptor, ionotropic, kainate 1	Response to statin therapy	75	rs9305406-G (0.2)	Response to statin therapy	Neuropathy, diabetic; Pain, general; Pain, musculoskeletal, arthritis; Pain, neuropathic	LY-5456	
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	Cognitive performance	39	rs2160519-? (0.06)	Cognitive performance	Alzheimer's disease; Depression, general; Depression, major depressive disorder; Haemorrhage, subarachnoid; Huntington's disease; Neuropathy, diabetic; Pain, general; Pain, neuropathic; Pain, post-operative; Parkinson's disease	ED-1529; EVT-101; EVT-103; MK-0657; NMDA NR2B subtype antagonists, AstraZeneca; NR2B antagonists, Merck; NR2B antagonists, NeurOp; NR2B antagonists, NeurOp-2; RG-1; Latrepirdine; Radiprod	
GRM7	glutamate receptor, metabotropic 7	Panic disorder	10	rs3749380-? (0.25)	Panic disorder	Addiction, alcohol; Depression, general; Post-traumatic stress disorder	AMN-082, MGLuR7 modulator, Add	
GRM7	glutamate receptor, metabotropic 7	Major depressive disorder	34	rs9870680-T (0.44)	Major depressive disorder	Addiction, alcohol; Depression, general; Post-traumatic stress disorder	AMN-082, MGLuR7 modulator, Add	
HAVCR1	hepatitis A virus cellular receptor 1	LDL cholesterol	42	rs1501908-G (0.37)	LDL cholesterol	Cancer, ovarian; Cancer, renal	CDX-0	
HBB	hemoglobin, beta	Malaria	3	rs11036238-? (0.14)	Malaria	Anaemia, sickle cell; Anaemia, unspecified; Thalassemia	AN-10; Aviheme; Pharmaprojects No. 4728; Pharmaprojects No. 4769; Pharmaprojects No. 5041; Thalagen; VX-366; Arginine butyrate; Globin gene therapy, Bluebird; Sickle cell therapy, Tapestry; Velares	
HCRTR2	hypocretin (orexin) receptor 2	HIV-1 control	25	rs9367630-? (NR)	HIV-1 control	Addiction, drug, unspecified; Anxiety, general; Arthritis, rheumatoid; Chronic obstructive pulmonary disease; Insomnia; Sleep disorder, general	649868; CR-5542; Almorexant; Orexin 1/2 antagonist, Heptares; Orexin 1/2 inhibitors, Evotec; Orexin 2R modulator, Addex; Suvorex	

Table 1		Strongest				New suggested		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	indication	indication		indications		drugs	
HFE2	hemochromatosis type 2 (juvenile)	Coronary heart disease	78	2-SNP haplotype-1 ((CC))	Coronary heart disease			Anaemia, unspecified		Anaemia of inflammation therapy, Is	
HLA-B	major histocompatibility complex, class I, B	HIV-1 control	25	rs2395029-? (NR), rs2395029-G (0.032), rs2395029-G (0.048), rs25233590-C (0.164), rs25233608-? (0.37), rs25233608-G (0.326)	HIV-1 control			Cancer, colorectal; Cancer, head and neck; Cancer, melanoma		Velimogene aliplasm	
HLA-B	major histocompatibility complex, class I, B	Vitiligo	25	rs11966200-A (0.06)	Vitiligo			Cancer, colorectal; Cancer, head and neck; Cancer, melanoma		Velimogene aliplasm	
HLA-B	major histocompatibility complex, class I, B	Drug-induced liver injury	7	rs2395029-? (0.05)	Drug-induced liver injury			Cancer, colorectal; Cancer, head and neck; Cancer, melanoma		Velimogene aliplasm	
HLA-B	major histocompatibility complex, class I, B	Multiple sclerosis	59	rs2523393-A (0.59)	Multiple sclerosis			Cancer, colorectal; Cancer, head and neck; Cancer, melanoma		Velimogene aliplasm	

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Table 1					
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication
HTR1A	5-hydroxytryptamine (serotonin) receptor 1A	Body mass index	70	rs255414-A (0.81)	Body mass index
					Current indications
					All drugs
					1192U90; ACN131; AL-8309A; AV-965; CM-2395; DSP-1053; DU-125530; ETI-0001; Lu-36-274; LuAA21004 (tablet); NPT-500; OPC-34712; Org-13011; PEL-576; PF-217830; Pharmaprojects No. 5019; RGH-1756; RGH-1757; Rec 15-3079; SLV-314; SRA-444; TGFK-08AA; Adoprazine; Alnespirone; Aripiprazole; Aripiprazole (once-weekly); Aripiprazole IM depot; Aripiprazole, Alkermes; Aripiprazole, ODT; Aripiprazole, RapidFilm; Befiradol; Buspirone; Buspirone + melatonin, BrainCells; Buspirone, Acrux; Buspirone, Arcturus; Buspirone, Biovail; Eltoprazine; Eptapirone maleate; Espindolol; Flesinoxan; Fibanserin; Gepirone; Ipsapirone; Levorphanol, TheraQuest; Lurasidone hydrochloride; Naluzotan; Pardoprunox; Piclozotan; Quetiapine fumarate, SR; Repinotan hydrochloride; Robalzotan tartrate hydrate; Sumanitrole; Tandospirone; Urapidil; Vilazodone; Xaliproden hydrochloride; Ziprasido

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	Cardiac hypertrophy	22	rs1575891-? (NR)	Cardiac hypertrophy	Addiction, alcohol; Addiction, cocaine; Allergy, general; Alzheimer's disease; Anorexia nervosa; Anxiety, general; Attention deficit hyperactivity disorder; Autism; Depression, bipolar; Depression, general; Dyskinesia, major depressive disorder; Fibromyalgia; Fibrosis, general; Generalized anxiety disorder; Glaucoma; Hypertension, general; Hypertension, pulmonary; Infarction, cerebral; Inflammatory bowel disease, general; Insomnia; Mental retardation; Migraine; Obsessive-compulsive disorder; Pain, general; Pancreatitis; Panic disorder; Parkinson's disease; Peripheral vascular disease; Post-traumatic stress disorder; Psychosis, bipolar; Psychosis, general; Schizophrenia; Sexual dysfunction, female; Sleep disorder, general; Thrombosis, arterial; Thrombosis, general; Tourette's syndrome; Transplant rejection, general; Venous insufficiency	5-HT2A antagonists, Aventis-2; 53711; 55284; BVT-28949; F-94116-CN; ITI-007; LY-2624803; MT210; N-desmethyloclozapine; OPC-34712; PF-217830; SL-65.0472; UMN-02; YKP-1447; Antidepressants, Green Cross; Aptazapine; Aripiprazole; Aripiprazole (once-weekly); Aripiprazole IM depot; Aripiprazole, Alkermes; Aripiprazole, ODT; Aripiprazole, RapidFilm; Asenapine maleate; Cyclobenzaprine, TONIX; Deramciclane fumarate; Eplivanserin; Etoperidone; Fananserin; Fibanserin; Ifeanserin, Ventrus; Iloperidone; Iloperidone, depot; Ketanserin; Lubazodone hydrochloride; Lurasidone hydrochloride; Mianserin; Nefazodone hydrochloride; Nelotanserin; Olanzapine; Olanzapine + pamoate acid; Olanzapine + zonisamide, Or; Olanzapine, Alkermes; Olanzapine, RAIM; Olanzapine, Zydis; Paliperidone palmitate; Perospirone; Pimavanserin tartrate; Pipamperone + citalopram, PNB; Pipamperone + risperidone, PharmaNeuroBoost; Risperidone; Risperidone 4wk long-acting injection (IM); Risperidone, Delpor; Risperidone, Medisorb; Risperidone, Nuvo Research; Risperidone, Quicklets; Sarpogrelate; Spiperone analogues; Temanogrel; Terguride, Ergonex; Volinanserin; Zicronapine; Ziprasido
HTR4	5-hydroxytryptamine (serotonin) receptor 4	Pulmonary function	13	rs11168048-T (0.58), rs3995090-C (0.41)	Asthma/Severe asthma/cough	Alzheimer's disease; Constipation; Diabetic complication, general; Dyspepsia; Dyspepsia, non-ulcer; Gastritis; Gastro-oesophageal reflux; Gastroparesis; Heart failure; Ileus; Irritable bowel syndrome; Motility dysfunction, GI, general; Nausea and vomiting, general; Nausea and vomiting, post-operative; Oesophagitis; Radio/chemotherapy-induced nausea and vomiting	5-HT4 partial agonist, pfizer; 5-HT4 partial agonists, concert; Cinitapride; Da-6650; Gi hypermotility disorders ther, movetis; Indisetrone; Levosulpiride; M-0003; M-0004; M-0014; Metoclopramide + lysine acetyl; Metoclopramide, diffucap; Metoclopramide, mdrna; Metoclopramide, nasal spray, evoke; Metoclopramide, valeant pharmaceuticals; Metoclopramide-zydis, salix; Mosapride; Naronapride; Omeprazole + cinitapride er, zyodus; Pantoprazole + cinitapride er, zyodus; Prucalopride; Prx-03140; Rq-10; Rq-9; Ser-103; Suvn-91052; Tegaserod maleate; Velusetrag; Yko-10811

Table 1		Strongest						
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs	
ICAM3	intercellular adhesion molecule 3	Crohn's disease	83	rs12720356-G (0.08)	Crohn's disease	Cancer, leukaemia, acute myelogenous; Crohn's disease	IC	
ICOS	inducible T-cell co-stimulator	Celiac disease	65	rs4675374-A (0.22)	Celiac disease	Lupus erythematosus, systemic	MEDI-570	
ICOS	inducible T-cell co-stimulator	Alopecia areata	11	rs1024161-A (0.40)	Alopecia areata	Lupus erythematosus, systemic	MEDI-5	
ICOSLG	inducible T-cell co-stimulator ligand	Celiac disease	65	rs4819388-? (0.72)	Celiac disease	Lupus erythematosus, systemic	AMG-5	
ICOSLG	inducible T-cell co-stimulator ligand	Crohn's disease	83	rs762421-G (0.39)	Crohn's disease	Lupus erythematosus, systemic	AMG-5	
ICOSLG	inducible T-cell co-stimulator ligand	Ulcerative colitis	96	rs2838519-G (0.39)	Ulcerative colitis	Lupus erythematosus, systemic	AMG-5	
IDS	iduronate 2-sulfatase	Cognitive test performance	33	rs530501-? (NR)	Cognitive test performance	Mucopolysaccharidosis II	JR-032; Idursulfa	
IFNG	interferon, gamma	Ulcerative colitis	96	rs1558744-A (0.38), rs1558744-A (NR), rs7134599-A (0.39)	Ulcerative colitis	Arthritis, rheumatoid; Cachexia; Cancer, basal cell; Cancer, liver; Cancer, lymphoma, B-cell; Cancer, lymphoma, T-cell; Cancer, melanoma; Cancer, renal; Crohn's disease; Glomerulonephritis; Lupus erythematosus, cutaneous; Lupus erythematosus, systemic; Lupus nephritis; Multiple sclerosis, general; Psoriasis	AMG-811; Ad-IFNgamma; Anti-IFN-gamma MAb, Solvay; Fontolizumab; Interferon gamma, A5 Laboratori	
IGF1	insulin-like growth factor 1 (somatomedin C)	Fasting insulin-related traits	2	rs35767-G (0.85)	Fasting insulin-related traits	Acromegaly; Amyotrophic lateral sclerosis; Autism; Ischaemia, cerebral; Macular degeneration, age-related, wet; Retinopathy, diabetic	ATL-1103; CERE-135; IGF-1 neurological therapy, Braasch; Pharmaprojects No. 58	
IGF1	insulin-like growth factor 1 (somatomedin C)	Fasting glucose-related traits	18	rs35767-G (0.85)	Fasting glucose-related traits	Acromegaly; Amyotrophic lateral sclerosis; Autism; Ischaemia, cerebral; Macular degeneration, age-related, wet; Retinopathy, diabetic	ATL-1103; CERE-135; IGF-1 neurological therapy, Braasch; Pharmaprojects No. 58	
IL10	interleukin 10	Type 1 diabetes	50	rs3024505-? (0.83)	Type 1 diabetes	Arthritis, rheumatoid; Infection, Ebola virus; Infection, Marburg virus; Inflammatory bowel disease, general; Psoriasis	54197; EG-10; HMPL-011; Autoimmune therapy, Epidy	

Table 1		Strongest SNP-Risk Allele (frequency)			Current indications			All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	New suggested indication					
IL10	interleukin 10	Crohn's disease	83	Crohn's disease	Arthritis, rheumatoid; Infection, Ebola virus; Infection, Marburg virus; Inflammatory bowel disease, general; Psoriasis			54197; EG-10; HMPL-011; Autoimmune therapy, Epidy	
IL10	interleukin 10	Behcet's disease	3	Behcet's disease	Arthritis, rheumatoid; Infection, Ebola virus; Infection, Marburg virus; Inflammatory bowel disease, general; Psoriasis			54197; EG-10; HMPL-011; Autoimmune therapy, Epidy	
IL12A	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	Celiac disease	65	Celiac disease	Arthritis, rheumatoid; Cancer, brain; Cancer, colorectal; Cancer, fallopian tube; Cancer, head and neck; Cancer, melanoma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Crohn's disease; Infection, hepatitis-B virus; Multiple sclerosis, general; Poisoning, radiation; Psoriasis			EGEN-001; IL-12 + IFN-alpha gene ther, Ino; Briakinumab; Cancer gene therapy, Intrexon; Hepatitis-B DNA vaccine, Genexine; Interleukin-12, Neumedicin	
IL12A	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	Primary biliary cirrhosis	26	Primary biliary cirrhosis	Arthritis, rheumatoid; Cancer, brain; Cancer, colorectal; Cancer, fallopian tube; Cancer, head and neck; Cancer, melanoma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Crohn's disease; Infection, hepatitis-B virus; Multiple sclerosis, general; Poisoning, radiation; Psoriasis			EGEN-001; IL-12 + IFN-alpha gene ther, Ino; Briakinumab; Cancer gene therapy, Intrexon; Hepatitis-B DNA vaccine, Genexine; Interleukin-12, Neumedicin	
IL12B	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	Crohn's disease	83	Crohn's disease	Arthritis, psoriatic; Arthritis, rheumatoid; Atherosclerosis; Cancer, brain; Cancer, colorectal; Cancer, fallopian tube; Cancer, head and neck; Cancer, melanoma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cirrhosis, primary biliary; Crohn's disease; Infection, hepatitis-B virus; Inflammatory bowel disease, general; Multiple sclerosis, general; Palmoplantar pustulosis; Poisoning, radiation; Psoriasis; Sarcoidosis			CEP-37248; CI-201; EGEN-001; FM-202; GX-P04; IL-12 + IFN-alpha gene ther, Ino; Briakinumab; Cancer gene therapy, Intrexon; Hepatitis-B DNA vaccine, Genexine; Interleukin-12, Neumedicines; Ustekinumab; Ustekinumab, BioXpre	

Table 1			Strongest					All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications			
IL12RB2	interleukin 12 receptor, beta 2	Primary biliary cirrhosis	26	rs17129789-C (0.18), rs3790567-A (0.232), rs3790567-A (0.24)	Primary biliary cirrhosis	Arthritis, rheumatoid; Cancer, lymphoma, T-cell; Cancer, melanoma; Cancer, neuroendocrine, Merkel cell carcinoma; Cancer, renal; Cancer, sarcoma, Kaposi's; Crohn's disease; Immunodeficiency, IgG deficiency; Infection, HIV/AIDS; Infection, hepatitis-C virus; Multiple sclerosis, general; Psoriasis	HIV DNA vaccine, Dong-A/Genexine; IL-12, OncoSec Medical; IL-2 + IL-12, Roche; Apilimod mesylate; Interleukin-12, Wye		
IL12RB2	interleukin 12 receptor, beta 2	Behcet's disease	3	rs1495965-G (0.51), rs924080-? (NR)	Behcet's disease	Arthritis, rheumatoid; Cancer, lymphoma, T-cell; Cancer, melanoma; Cancer, neuroendocrine, Merkel cell carcinoma; Cancer, renal; Cancer, sarcoma, Kaposi's; Crohn's disease; Immunodeficiency, IgG deficiency; Infection, HIV/AIDS; Infection, hepatitis-C virus; Multiple sclerosis, general; Psoriasis	HIV DNA vaccine, Dong-A/Genexine; IL-12, OncoSec Medical; IL-2 + IL-12, Roche; Apilimod mesylate; Interleukin-12, Wye		
IL13	interleukin 13	Psoriasis	30	rs20541-G (0.79)	Psoriasis	Addiction, nicotine; Asthma; Cancer, brain; Cancer, lymphoma, Hodgkin's; Chronic obstructive pulmonary disease; Colitis, ulcerative; Crohn's disease; Fibrosis, pulmonary, idiopathic; Rhinitis, allergic, seasonal; Wound healing	56076; IL-13 siRNAs, Allerna Therapeutics; QAX-576; SAR-156597; SB-313; Anrukizumab; Lebrikizumab; Nadolol, Inverseon; Tralokinum		
IL15	interleukin 15	Response to treatment for acute lymphoblastic leukemia	8	rs17007695-C (NR)	Response to treatment for acute lymphoblastic leukemia	Arthritis, rheumatoid; Inflammation, general; Psoriasis	AMG-714; DISC-02		
IL18R1	interleukin 18 receptor 1	Celiac disease	65	rs13015714-C (NR), rs917997-A (0.24)	Celiac disease	Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, renal; Epilepsy, partial (focal, local); Inflammation, general; Psoriasis	VX-765; Iboctadekin; Iboctadekin + doxorubicin; Iboctadekin + rituxim		
IL18R1	interleukin 18 receptor 1	Asthma	19	rs3771166-G (0.62)	Asthma	Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, renal; Epilepsy, partial (focal, local); Inflammation, general; Psoriasis	VX-765; Iboctadekin; Iboctadekin + doxorubicin; Iboctadekin + rituxim		

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest	New suggested indication	Current indications	All drugs
				SNP-Risk Allele (frequency)			
IL1A	interleukin 1, alpha	Endometriosis	4	rs6542095-C (0.72)	Endometriosis	Arthritis, rheumatoid; Atherosclerosis; Cancer, general; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, chronic myelomonocytic; Cancer, liver; Cancer, lymphoma, general; Cancer, solid, general; Diabetes, Type 2; Idiopathic myelofibrosis; Myelodysplastic syndrome; Reperfusion injury; Restenosis; Thrombosis, general	MABp1; Arthritis therapy, NanoSmart
IL1R2	interleukin 1 receptor, type II	Ulcerative colitis	96	rs2310173-T (0.46)	Ulcerative colitis	Anaemia, renal disease-induced; Arthritis, juvenile; Arthritis, osteo; Arthritis, rheumatoid; Cancer, biliary; Cancer, breast; Cancer, colorectal; Cancer, leukaemia, acute myelogenous; Cancer, lung, non-small cell; Cancer, lymphoma, Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, pancreatic; Cancer, solid, general; Chronic obstructive pulmonary disease; Diabetes, Type 2; Familial cold autoinflammatory syndrome; Hyperuricaemia; Idiopathic myelofibrosis; Inflammation, general; Irritable bowel syndrome; Muckle-Wells syndrome; Mucositis, general; Polycythaemia vera; Thrombocythaemia; Thrombophlebitis	9683; AMG-108; ARRY-438162; CDP-484; PMI-005; Givinostat; Rilonace
IL2	interleukin 2	Type 1 diabetes	50	rs4505848-? (NR)	Type 1 diabetes	Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, liver; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, soft tissue; Dysplasia, cervical; Infection, HIV/AIDS; Infection, cytomegalovirus; Infection, human papilloma virus	IL-2 Cancer Gene Medicine; IL-2 gene therapy, Targeted Genetics; NTC-121; Reximmune-C; TG-4010; Tipapkinogene sovaciv

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
IL2	interleukin 2	Celiac disease	65	rs13151961-? (0.86), rs6822844-C (0.81), rs6822844-G (0.82)	Celiac disease	Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, liver; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, soft tissue; Dysplasia, cervical; Infection, HIV/AIDS; Infection, cytomegalovirus; Infection, human papilloma virus
IL2	interleukin 2	Rheumatoid arthritis	49	rs13119723-A (0.15)	Rheumatoid arthritis	Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, liver; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, soft tissue; Dysplasia, cervical; Infection, HIV/AIDS; Infection, cytomegalovirus; Infection, human papilloma virus
IL2	interleukin 2	Alopecia areata	11	rs7682241-A (0.33)	Alopecia areata	Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, liver; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, soft tissue; Dysplasia, cervical; Infection, HIV/AIDS; Infection, cytomegalovirus; Infection, human papilloma virus
IL2	interleukin 2	Ulcerative colitis	96	rs17388568-A (0.27)	Ulcerative colitis	Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, liver; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, soft tissue; Dysplasia, cervical; Infection, HIV/AIDS; Infection, cytomegalovirus; Infection, human papilloma virus
IL21R	interleukin 21 receptor	Bone mineral density	42	rs8057551-G (0.32)	Bone mineral density	Arthritis, rheumatoid; Cancer, colorectal; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, ovarian; Cancer, renal; Crohn's disease; Lupus erythematosus, systemic
					All drugs	
					IL-2 Cancer Gene Medicine; IL-2 gene therapy, Targeted Genetics; NTC-121; Reximmune-C; TG-4010; Tipapkinogene sovaciv	
					IL-2 Cancer Gene Medicine; IL-2 gene therapy, Targeted Genetics; NTC-121; Reximmune-C; TG-4010; Tipapkinogene sovaciv	
					IL-2 Cancer Gene Medicine; IL-2 gene therapy, Targeted Genetics; NTC-121; Reximmune-C; TG-4010; Tipapkinogene sovaciv	
					ATR-107; NNC-114-0005; Denenickok	

Table 1		Strongest SNP-Risk Allele (frequency)			Current indications			All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	New suggested indication					
IL23R	interleukin 23 receptor	Ankylosing spondylitis	7	Ankylosing spondylitis	Arthritis, rheumatoid; Inflammatory bowel disease, general; Multiple sclerosis, general; Psoriasis			ATX-3105; FM-2	
IL23R	interleukin 23 receptor	Crohn's disease	83	Crohn's disease	Arthritis, rheumatoid; Inflammatory bowel disease, general; Multiple sclerosis, general; Psoriasis			ATX-3105; FM-2	
IL23R	interleukin 23 receptor	Inflammatory bowel disease	17	Inflammatory bowel disease	Arthritis, rheumatoid; Inflammatory bowel disease, general; Multiple sclerosis, general; Psoriasis			ATX-3105; FM-2	
IL23R	interleukin 23 receptor	Behcet's disease	3	Behcet's disease	Arthritis, rheumatoid; Inflammatory bowel disease, general; Multiple sclerosis, general; Psoriasis			ATX-3105; FM-2	
IL27	interleukin 27	Type 1 diabetes	50	Type 1 diabetes	Adrenoleukodystrophy; Arthritis, rheumatoid; Infection, HIV/AIDS; Infection, herpes virus, unspecified; Infection, rabies; Infection, varicella zoster virus; Multiple sclerosis, general; Myasthenia gravis			RPI-7	

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
IL27	interleukin 27	Crohn's disease	83	rs151181-G (0.39)	Crohn's disease	Adrenoleukodystrophy; Arthritis, rheumatoid; Infection, HIV/AIDS; Infection, herpes virus, unspecified; Infection, rabies; Infection, varicella zoster virus; Multiple sclerosis, general; Myasthenia gravis
IL27	interleukin 27	Inflammatory bowel disease	17	rs8049439-G (0.37)	Inflammatory bowel disease	Adrenoleukodystrophy; Arthritis, rheumatoid; Infection, HIV/AIDS; Infection, herpes virus, unspecified; Infection, rabies; Infection, varicella zoster virus; Multiple sclerosis, general; Myasthenia gravis
IL28RA	interleukin 28 receptor, alpha (interferon, lambda receptor)	Psoriasis	30	rs4649203-A (0.73)	Psoriasis	Infection, hepatitis-B virus; Infection, hepatitis-C virus
						All drugs
						RPI-7
						RPI-7
						Interleukin-29, ZymoGeneti

Table 1					
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication
IL2RA	interleukin 2 receptor, alpha	Crohn's disease	83	rs12722489-C (0.85)	Crohn's disease
					Current indications Arthritis, rheumatoid; Asthma; Burns; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, nasopharyngeal; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general; Cancer, squamous cell; Cancer, urethral; Colitis, ulcerative; Diabetes, Type 1; Dysplasia, cervical; Eczema, atopic; Endometriosis; Head trauma; Infection, Brucella; Infection, Chlamydia; Infection, HIV/AIDS; Infection, bone; Infection, cytomegalovirus; Infection, dermatological; Infection, gynaecological; Infection, haemorrhagic fever; Infection, hepatitis-C virus; Infection, herpes simplex virus; Infection, intra-abdominal, unspecified; Infection, meningitis, viral; Infection, pneumonia, hospital-acquired; Infection, tuberculosis; Infection, urinary tract, unspecified; Infection, varicella zoster virus; Inflammation, prostate; Lupus erythematosus, systemic; Multiple sclerosis, general; Multiple sclerosis, progressive, secondary; Multiple sclerosis, relapsing-remitting; Nephritis, general; Pancreatitis; Psoriasis; Sepsis; Sinusitis; Transplant rejection, bone marrow; Transplant rejection, general; Ulcer, diabetic; Ulcer, gastric; Uveitis; Wound healing
					All drugs ALT-801; CYT-91000; EMD-273063; IL-2 + IL-12, Roche; MT-204; NHS-IL2-LT; PRO-1556; WuTac; Aldesleukin; Aldesleukin, Zenotech; Anti-IL2 receptor MAb, Seragen; Basiliximab; Celmoleukin; Daclizumab; Darleukin; Denileukin difitox; Interleukin-2 inhibitors, Sune; Interleukin-2, 2nd-gen, 3SBio; Interleukin-2, Ajinomoto; Interleukin-2, Biotech; Interleukin-2, Medusa, Flamel; Interleukin-2, Novartis; Interleukins, Cel-Sci; Teceleukin; Thymotrinan; Tucotuzumab celmoleuk

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
IL2RA	interleukin 2 receptor, alpha	Alopecia areata	11	rs3118470-G (0.30)
				Alopecia areata
				Arthritis, rheumatoid; Asthma; Burns; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, nasopharyngeal; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general; Cancer, squamous cell; Cancer, urethral; Colitis, ulcerative; Diabetes, Type 1; Dysplasia, cervical; Eczema, atopic; Endometriosis; Head trauma; Infection, Brucella; Infection, Chlamydia; Infection, HIV/AIDS; Infection, bone; Infection, cytomegalovirus; Infection, dermatological; Infection, gynaecological; Infection, haemorrhagic fever; Infection, hepatitis-C virus; Infection, herpes simplex virus; Infection, intra-abdominal, unspecified; Infection, meningitis, viral; Infection, pneumonia, hospital-acquired; Infection, tuberculosis; Infection, urinary tract, unspecified; Infection, varicella zoster virus; Inflammation, prostate; Lupus erythematosus, systemic; Multiple sclerosis, general; Multiple sclerosis, progressive, secondary; Multiple sclerosis, relapsing-remitting; Nephritis, general; Pancreatitis; Psoriasis; Sepsis; Sinusitis; Transplant rejection, bone marrow; Transplant rejection, general; Ulcer, diabetic; Ulcer, gastric; Uveitis; Wound healing
				All drugs
				ALT-801; CYT-91000; EMD-273063; IL-2 + IL-12, Roche; MT-204; NHS-IL2-LT; PRO-1556; WuTac; Aldesleukin; Aldesleukin, Zenotech; Anti-IL2 receptor MAb, Seragen; Basiliximab; Celmoleukin; Daclizumab; Darleukin; Denileukin difitox; Interleukin-2 inhibitors, Sune; Interleukin-2, 2nd-gen, 3SBio; Interleukin-2, Ajinomoto; Interleukin-2, Biotech; Interleukin-2, Medusa, Flamel; Interleukin-2, Novartis; Interleukins, Cel-Sci; Teceleukin; Thymotrinan; Tucotuzumab celmoleuk

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
IL2RA	interleukin 2 receptor, alpha	Vitiligo	25	rs706779-A (0.535)	Vitiligo	Arthritis, rheumatoid; Asthma; Burns; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, nasopharyngeal; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, solid, general; Cancer, squamous cell; Cancer, urethral; Colitis, ulcerative; Diabetes, Type 1; Dysplasia, cervical; Eczema, atopic; Endometriosis; Head trauma; Infection, Brucella; Infection, Chlamydia; Infection, HIV/AIDS; Infection, bone; Infection, cytomegalovirus; Infection, dermatological; Infection, gynaecological; Infection, haemorrhagic fever; Infection, hepatitis-C virus; Infection, herpes simplex virus; Infection, intra-abdominal, unspecified; Infection, meningitis, viral; Infection, pneumonia, hospital-acquired; Infection, tuberculosis; Infection, urinary tract, unspecified; Infection, varicella zoster virus; Inflammation, prostate; Lupus erythematosus, systemic; Multiple sclerosis, general; Multiple sclerosis, progressive, secondary; Multiple sclerosis, relapsing-remitting; Nephritis, general; Pancreatitis; Psoriasis; Sepsis; Sinusitis; Transplant rejection, bone marrow; Transplant rejection, general; Ulcer, diabetic; Ulcer, gastric; Uveitis; Wound healing	ALT-801; CYT-91000; EMD-273063; IL-2 + IL-12, Roche; MT-204; NHS-IL2-LT; PRO-1556; WuTac; Aldesleukin; Aldesleukin, Zenotech; Anti-IL2 receptor MAb, Seragen; Basiliximab; Celmoleukin; Dacizumab; Darleukin; Denileukin difitox; Interleukin-2 inhibitors, Sune; Interleukin-2, 2nd-gen, 3SBio; Interleukin-2, Ajinomoto; Interleukin-2, Biotech; Interleukin-2, Medusa, Flamel; Interleukin-2, Novartis; Interleukins, Cel-Sci; Teceleukin; Thymotrinan; Tucotuzumab celmoleuk

Table 1		Strongest			New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)						
IL2RB	interleukin 2 receptor, beta	Asthma	19	rs2284033-G (0.56)	Asthma		Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, T-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, solid, general		CYT-91000; NHS-IL2-	
IL2RB	interleukin 2 receptor, beta	Rheumatoid arthritis	49	rs743777-G (NR)	Rheumatoid arthritis		Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, T-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, solid, general		CYT-91000; NHS-IL2-	
IL3	interleukin 3 (colony-stimulating factor, multiple)	Crohn's disease	83	rs12521868-T (0.42)	Crohn's disease		Cancer, prostate; Cancer, sarcoma, general		IL-3 gene therapy, Crucell; Prostate cancer ther, V	
IL3RA	interleukin 3 receptor, alpha (low affinity)	Schizophrenia	33	rs4129148-C (NR)	Schizophrenia		Anaemia, aplastic; Anaemia, radio/chemotherapy-induced; Arthritis, rheumatoid; Cancer, breast; Cancer, general; Cancer, haematological, general; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Immunodeficiency, general; Myelodysplastic syndrome; Neutropenia, general; Radio/chemotherapy-induced injury, bone marrow, thrombocytopenia; Radio/chemotherapy-induced injury, general		CSL-360; CSL-362; PEG-interleukin-3, Wyeth; SL-401; SL-501; Anti-IL3 MAb, SuppreMol; Daniplestim; Leridistim; Muplestim, Cangene; Muplestim, Wye	
IL6	interleukin 6 (interferon, beta 2)	Dialysis-related mortality	31	rs17364464-? (0.08)	Dialysis-related mortality		Arthritis, general; Arthritis, rheumatoid; Cachexia; Cancer fatigue; Cancer, colorectal; Cancer, haematological, general; Cancer, head and neck; Cancer, lung, non-small cell; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, solid, general; Castleman's disease; Crohn's disease; Inflammation, general; Lupus erythematosus, cutaneous; Lupus erythematosus, systemic; Lupus nephritis; Waldenström's hypergammaglobulinaemia		ALD-518; FM-101; OPR-003; Anti-IL-6 MAb, MedImmune; Olokizumab (IV); Siltuximab; Sirukum	

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
IL6R	interleukin 6 receptor	Pulmonary function traits	8	rs4129267-? (NR)	Pulmonary function traits	Ankylosing spondylitis; Arthritis, juvenile; Arthritis, rheumatoid; Asthma; Cancer, biliary; Cancer, breast; Cancer, colorectal; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, myeloma; Cancer, pancreatic; Cancer, sarcoma, Kaposi's; Cancer, solid, general; Castleman's disease; Chronic obstructive pulmonary disease; Colitis, ulcerative; Conjunctivitis, inflammatory; Crohn's disease; Heart failure; Infection, HIV/AIDS; Inflammation, general; Inflammatory bowel disease, general; Irritable bowel syndrome; Lupus erythematosus, systemic; Psoriasis; Radio/chemotherapy-induced injury, bone marrow, neutropenia; Radio/chemotherapy-induced injury, bone marrow, induced injury, bone marrow, thrombocytopenia; Rhinitis, allergic, general; Thrombocytopenia, general; Thrombocytopenic purpura; Urticaria
IL7	interleukin 7	Longevity	23	rs2717536-A (0.14)	Longevity	Cancer, breast; Cancer, colorectal; Cancer, lung, general; Cancer, melanoma; Cancer, renal
IL7R	interleukin 7 receptor	Type 1 diabetes	50	rs6897932-G (0.71)	Type 1 diabetes	Cancer, general; Immunodeficiency, general
IL7R	interleukin 7 receptor	Ulcerative colitis	96	rs3194051-G (0.27)	Ulcerative colitis	Cancer, general; Immunodeficiency, general
IL7R	interleukin 7 receptor	Primary biliary cirrhosis	26	rs860413-A (0.72)	Primary biliary cirrhosis	Cancer, general; Immunodeficiency, general
IL7R	interleukin 7 receptor	Multiple sclerosis	59	rs6897932-C (0.75), rs931555-? (NR)	Multiple sclerosis	Cancer, general; Immunodeficiency, general
INS	insulin	Prostate cancer	30	rs7127900-A (0.20)	Prostate cancer	Diabetes, Type 1; Diabetes, Type 2
					All drugs	
					ALX-0061; AM-87; ARRY-438162; IL-6 antagonists, Protonist Therapeutics; Pharmaprojects No. 6000; SA-237; Interferon alpha + oncostatin M, Hepacyl Therapeutics; Interleukin-6 fusion toxin, Lig; Interleukin-6 receptor MAb, Ch; Interleukin-6, Ajinomoto; Interleukin-6, Cangene; Interleukin-6, Wyeth; Medroxyprogesterone, Inkine; Sarilumab; Tocilizumab; Tocilizumab, BioXpress; Vesnarino	
					MGN-16	
					IL-7-Dap 389 fusion toxin; Interleukin-7, Cytheris; Interleukin-7, IC Innovatio	
					IL-7-Dap 389 fusion toxin; Interleukin-7, Cytheris; Interleukin-7, IC Innovatio	
					IL-7-Dap 389 fusion toxin; Interleukin-7, Cytheris; Interleukin-7, IC Innovatio	
					IL-7-Dap 389 fusion toxin; Interleukin-7, Cytheris; Interleukin-7, IC Innovatio	
					EG-02; Encellin XP; NNC-0123-0000-0338; Insulin, targeted, Merck & Co; Islet cells, TheraCys; Proinsulin, BayHill Therapeuti	

Table 1					
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication
INSR	insulin receptor	Diabetic retinopathy	34	rs2115386-C (0.55)	Diabetic retinopathy
					Current indications
					All drugs
					14920; AGT-181; CJC-1525; EML-16257; HinsBet; Insulin Aspart; Insulin Aspart, biphasic-2, No; Insulin Aspart, biphasic-3, Novo Nordisk; KRX-613; NN-1218; NN-1952; NNC 0100-0454/ NNC 90-1170; P30; PRO-001, ProRetina; SIA-II Insulin, Extended Delivery; XMetA; XMetS; Antidiabetic, Fate Therapeutics; Insulin + GLP-1, Ascendis Pharma; Insulin Aspart, biphasic, Novo Nordisk; Insulin analogue, Lilly; Insulin aspart, Biocon; Insulin degludec; Insulin degludec + insulin aspart; Insulin detemir; Insulin glargine; Insulin glargine + lixisenatide; Insulin glargine, Biocon; Insulin glargine, Biodel; Insulin glargine, Gan & Lee Pharmaceutical; Insulin glargine, Lilly; Insulin glargine, Wockhardt; Insulin glulisine; Insulin lispro, Biocon; Insulin mimetic, Biota; Insulin, AERx; Insulin, Access; Insulin, Advancell; Insulin, Alkermes, inhaled; Insulin, Apicrus Biosciences; Insulin, BEODAS; Insulin, Chiron; Insulin, Cpex, intranasal; Insulin, Ferring Pharma; Insulin, Genentech, recombinant; Insulin, Medusa, Flamel-2; Insulin, Novo Nordisk; Insulin, Orin; Insulin, PharmFilm; Insulin, Phosphagenics; Insulin, PolyXen, Lipoxen; Insulin, ProStrakan; Insulin, Sanofi Aventis; Insulin, SemBioSys; Insulin, Spiros; Insulin, Technosphere, Mannkind; Insulin, Wockhardt; Insulin, Zymo, recombinant; Insulin, basal, Lilly; Insulin, basal, adjustable, Biodel; Insulin, buccal, Generex; Insulin, hydrogel, Ascendis; Insulin, inhaled, Dance Pharma; Insulin, inhaled, Nektar; Insulin, monocomponent, Novo; Insulin, nasal, DelSite; Insulin, nasal, Novo Nordisk; Insulin, oral, Apollo; Insulin, oral, Biocon-2; Insulin, oral, Biolaxy; Insulin, oral, CM&D Pharma; Insulin, oral, Emisphere-2; Insulin, oral, Oramed; Insulin, oral, Oshadi Drug Administration; Insulin, rapid-acting analogue + PH20, Halozyme; Insulin, rapid-acting analogue, Biodel; Insulin, recombinant, Aventis; Insulin, regular human, Biodel; Insulin, short-acting regular + PH20, Halozyme; Insulin, sublingual, Biodel; Oral insulin, C

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
IRS1	insulin receptor substrate 1	Type 2 diabetes	61	rs7578326-A (NR)	Type 2 diabetes	Corneal injury; Glaucoma; Macular degeneration, age-related, general; Psoriasis; Retinopathy, diabetic; Retinopathy, general; Rosacea	Aganirsen (intravitreal)
IRS1	insulin receptor substrate 1	Type 2 diabetes and other traits	7	rs2943641-C (0.63)	Type 2 diabetes and other traits	Corneal injury; Glaucoma; Macular degeneration, age-related, general; Psoriasis; Retinopathy, diabetic; Retinopathy, general; Rosacea	Aganirsen (intravitreal)
ITGA11	integrin, alpha 11	Attention deficit hyperactivity disorder	45	rs7164335-? (NR)	Attention deficit hyperactivity disorder	Arthritis, osteo; Arthritis, rheumatoid	Alpha11A1 antagonist, Han
ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	Celiac disease	65	rs13010713-G (0.45)	Celiac disease	Alopecia, androgenic; Arthritis, rheumatoid; Asthma; Atherosclerosis; Cancer, haematological, general; Cancer, myeloma; Colitis, ulcerative; Crohn's disease; Eczema, atopic; Infection, HIV/AIDS; Infection, human papilloma virus; Inflammatory bowel disease, general; Irritable bowel syndrome; Multiple sclerosis, general; Multiple sclerosis, progressive, secondary; Multiple sclerosis, relapsing-remitting; Psoriasis; Radio/chemotherapy-induced alopecia; Radio/chemotherapy-induced injury, bone marrow, general	AS-101; BIO-1211; CDP-323; DW-908e; ELND-002; ISIS-107248; TBC-3342; TBC-772; TRK-170; VLA-4 inhibitors, Elan; VLA-4 antagonists, Uriach; Etrolizumab; Firategrast; Natalizumab; Natalizumab, BioXpress; Valategrast hydrochloride; Vedolizum
ITGA9	integrin, alpha 9	Nasopharyngeal carcinoma	9	rs189897-A (0.09)	Nasopharyngeal carcinoma	Bone disorder, general; Cancer, general; Immune disease, unspecified	Anti-alpha9 integrin MAbs, G
ITGAE	integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)	Attention deficit hyperactivity disorder	45	rs220470-? (NR)	Attention deficit hyperactivity disorder	Colitis, ulcerative	Etrolizum

Table 1		Strongest			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)			
ITGAM	integrin, alpha M (complement component 3 receptor 3 subunit)	Systemic lupus erythematosus	42	rs11150610-? (0.42), rs11574637-C (0.19), rs9888739-T (0.13)	Systemic lupus erythematosus	Asthma; Chronic obstructive pulmonary disease; Hepatic dysfunction, general	SN-18915; Dual LFA-1/Mac-1 antagonist, Hoffmann-La Roc
ITGB1	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	Depression-- quantitative trait	9	rs11009175-A (0.17)	Depression-- quantitative trait	Arthritis, osteo; Arthritis, rheumatoid; Asthma; Atherosclerosis; Cancer, bone; Cancer, colorectal; Cancer, liver; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, solid, general; Colitis, ulcerative; Crohn's disease; Inflammatory bowel disease, general; Irritable bowel syndrome; Macular degeneration, age-related, wet; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting	52363; BIO-1211; DI-17E6; DW-908e; Evatak; GBR-500; JSM-6427; PF-04605412; TBC-3342; TBC-772; TRK-170; TRK-720; VLA -4 inhibitors, Elan; VLA-4 antagonists, Uriach; Alpha11A1 antagonist, Hansa; Firatgrast; Natalizumab; Natalizumab, BioXpress; Valategrast hydrochloride; Volocixim
ITGB6	integrin, beta 6	Nephropathy	23	rs4664308-? (0.43)	Nephropathy	Cancer, bone; Cancer, colorectal; Cancer, endometrial; Cancer, liver; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, soft tissue; Cancer, solid, general; Diagnosis, cancer; Fibrosis, general; Fibrosis, pulmonary, idiopathic; Nephropathy, general	DI-17E6; STX-100; Integrin alphaV β 6 binding agent, CRT; Intetumum
ITGB6	integrin, beta 6	Type 2 diabetes	61	rs7593730-? (0.78)	Type 2 diabetes	Cancer, bone; Cancer, colorectal; Cancer, endometrial; Cancer, liver; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, soft tissue; Cancer, solid, general; Diagnosis, cancer; Fibrosis, general; Fibrosis, pulmonary, idiopathic; Nephropathy, general	DI-17E6; STX-100; Integrin alphaV β 6 binding agent, CRT; Intetumum

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
JAK2	Janus kinase 2	Crohn's disease	83	rs10758669-C (0.35)	Crohn's disease	Arthritis, rheumatoid; Cancer, breast; Cancer, colorectal; Cancer, general; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, solid, general; Hypertension, pulmonary; Idiopathic myelofibrosis; Myelodysplastic syndrome; Polycythaemia vera; Psoriasis; Thrombocythaemia; Thrombocytopenia, general; Thrombocytosis	AC-430; AEG-41174; AG-490; AMG-Jak2-01; AT-9283; AZ-Tak1; AZD-1480; CYT-387; GLPG-0634; INCB-16562; INCB-28050; LY-2784544; NS-018; ON-044580; SAR-302503; SB-1317; SB-1518; SGI-1252; Degrasyns; Lestaurtinib; Ruxolitinib; Tozasertib lacta
JAK2	Janus kinase 2	Myeloproliferative neoplasms	1	rs10974944-? (NR)	Myeloproliferative neoplasms	Arthritis, rheumatoid; Cancer, breast; Cancer, colorectal; Cancer, general; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, solid, general; Hypertension, pulmonary; Idiopathic myelofibrosis; Myelodysplastic syndrome; Polycythaemia vera; Psoriasis; Thrombocythaemia; Thrombocytopenia, general; Thrombocytosis	AC-430; AEG-41174; AG-490; AMG-Jak2-01; AT-9283; AZ-Tak1; AZD-1480; CYT-387; GLPG-0634; INCB-16562; INCB-28050; LY-2784544; NS-018; ON-044580; SAR-302503; SB-1317; SB-1518; SGI-1252; Degrasyns; Lestaurtinib; Ruxolitinib; Tozasertib lacta

Table 1		Strongest			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes	SNP Risk Allele (frequency)			
JAK2	Janus kinase 2	Ulcerative colitis	96	rs10758669-C (0.35), rs10758669-C (NR), rs10975003-C (0.19)	Ulcerative colitis	Arthritis, rheumatoid; Cancer, breast; Cancer, colorectal; Cancer, general; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, chronic myelomonocytic; Cancer, leukaemia, general; Cancer, liver; Cancer, lung, non-small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, solid, general; Hypertension, pulmonary; Idiopathic myelofibrosis; Myelodysplastic syndrome; Polycythaemia vera; Psoriasis; Thrombocythaemia; Thrombocytopenia, general; Thrombocytosis	AC-430; AEG-41174; AG-490; AMG-Jak2-01; AT-9283; AZ-Tak1; AZD-1480; CYT-387; GLPG-0634; INCB-16562; INCB-28050; LY-2784544; NS-018; ON-044580; SAR-302503; SB-1317; SB-1518; SGI-1252; Degrasyns; Lestaurtinib; Ruxolitinib; Tozasertib lacta
JUN	jun proto-oncogene	Cognitive performance	39	rs4601609-? (0.05)	Cognitive performance	Arthritis, osteo; Arthritis, rheumatoid; Cancer, basal cell; Cancer, breast; Cancer, prostate; Cancer, skin, general; Cushing's disease; Heart failure; Macular degeneration, age-related, general; Pain, general; Pain, neuropathic; Restenosis; Retinopathy, diabetic	DNAzymes, NSI; Dz-13; T-5224; Tarenflurbil, PAZ; Trilosta
KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	Mortality among heart failure patients	10	rs4979906-G (0.186)	Mortality among heart failure patients	Glaucoma; Impotence; Incontinence, urinary; Macular degeneration, age-related, dry; Oedema, macular, diabetic; Overactive bladder; Pollakisuria; Psychosis, general; Retinitis pigmentosa	NS-1619; NS-8; HMaxi-K; Isopropyl unoprosto

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	Type 2 diabetes	61	rs2237892-C (0.59), rs2237892-C (0.61), rs2237892-C (NR), rs2237895-C (0.33), rs2237897-C (0.34), rs231362-G (NR)	Type 2 diabetes	Fibrillation, atrial; Fibrillation, ventricular; Tachycardia, supraventricular
KIF11	kinesin family member 11	Type 2 diabetes	61	rs6583826-G (0.26)	Type 2 diabetes	Cancer, bladder; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, chronic myelomonocytic; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, neuroendocrine, pancreatic; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, solid, general; Cancer, squamous cell; Myelodysplastic syndrome
						All drugs
						Azimilide dhydrochlori
						4SC-205; ALN-VSP; ARQ-621; ARRY-520; AZD-4877; SB-743921; Ispinesib mesylate; Litrones

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Bipolar disorder	21	rs2537859-T (0.60)	Bipolar disorder	Alzheimer's disease; Anaemia, radio/chemotherapy-induced; Arthritis, rheumatoid; Asthma; Cancer, biliary; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, general; Cancer, gastrointestinal, stomach; Cancer, gastrointestinal, stromal; Cancer, haematological, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, mast cell; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, nasopharyngeal; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, general; Cancer, neuroendocrine, pancreatic; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, glial; Cancer, sarcoma, leiomyo; Cancer, sarcoma, soft tissue; Cancer, sarcoma, synovial; Cancer, solid, general; Cancer, testicular; Cancer, thyroid; Fibrosis, pulmonary; Fibrosis, pulmonary, idiopathic; Hypereosinophilic syndrome, idiopathic; Hypertension, pulmonary; Inflammation, general; Macular degeneration, age-related, wet; Mastocytosis;	AMG-191; DCC-2157; DCC-2618; DP-2514; ENMD-2076; KIT816 inhibitor, AB Science; OSI-930; PLX-3397; PLX-647; SU-14813; XL-820; XL-999; Amuvatinib; Ancestim; Axitinib; Cabozantinib; Cediranib; Dasatinib; Dovitinib lactate; Foretinib; Imatinib mesilate; Lenvatinib; Masitinib; Midostaurin; Motesanib diphosphate; Nilotinib; Pazopanib hydrochloride; Pazopanib hydrochloride (ophthalmic); Regorafenib; Sunitinib malate; Tandutinib; Tivozanib; Vatalan

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
KIT continued	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Bipolar disorder	21	rs2537859-T (0.60)	Bipolar disorder	Multiple sclerosis, general; Multiple sclerosis, progressive, primary; Multiple sclerosis, progressive, secondary; Myelodysplastic syndrome; Oedema, macular, diabetic; Polycythaemia vera; Psoriasis; Scleroderma; Stem cell mobilization; Transplant rejection, bone marrow	AMG-191; DCC-2157; DCC-2618; DP-2514; ENMD-2076; KIT816 inhibitor, AB Science; OSI-930; PLX-3397; PLX-647; SU-14813; XL-820; XL-999; Amuvatinib; Ancestim; Axitinib; Cabozantinib; Cediranib; Dasatinib; Dovitinib lactate; Foretinib; Imatinib mesilate; Lenvatinib; Masitinib; Midostaurin; Motesanib diphosphate; Nilotinib; Pazopanib hydrochloride; Pazopanib hydrochloride (ophthalmic); Regorafenib; Sunitinib malate; Tandutinib; Tivozanib; Vatalan
LAMC2	laminin, gamma 2	Systemic lupus erythematosus	42	rs525410-? (0.49)	Systemic lupus erythematosus	Cancer, breast; Cancer, colorectal; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic	CYN-1
LAMC2	laminin, gamma 2	Coronary heart disease	78	rs1028771-A (0.97)	Coronary heart disease	Cancer, breast; Cancer, colorectal; Cancer, lung, non-small cell; Cancer, ovarian; Cancer, pancreatic	CYN-1
LCAT	lecithin-cholesterol acyltransferase	Coronary heart disease	78	rs3729639-T (0.44)	Coronary heart disease	Atherosclerosis	AAV8-hLCAT, Merck &
LDLR	low density lipoprotein receptor	Coronary heart disease	78	rs1122608-G (0.77)	Coronary heart disease	Atherosclerosis; Cystic fibrosis; Hypercholesterolaemia; Hyperlipidaemia, general	COR-2; LDL-4X4; LDLr PLASmin DNA complexes; Pharmaprojects No. 5637; Axitrome; Gene therapy, Geno
LINGO1	leucine rich repeat and Ig domain containing 1	Essential tremor	1	rs9652490-G (0.23)	Essential tremor	Multiple sclerosis, general; Multiple sclerosis, progressive, secondary; Multiple sclerosis, relapsing-remitting	BIIB-033; LI33 PEG-Fab, Biogen Id
LIPA	lipase A, lysosomal acid, cholesterol esterase	Coronary heart disease	78	rs1412444-T (0.32), rs1412444-T (0.42)	Coronary heart disease	Atherosclerosis; Lysosomal acid lipase deficiency	Lysosomal acid lipase, Large S; Recombinant lysosomal acid lipase, Synageva BioPhar
LPAR3	lysophosphatidic acid receptor 3	Type 1 diabetes	50	rs1983853-? (NR)	Type 1 diabetes	Fibrosis, general	SAR-1008

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes					
LPL	lipoprotein lipase	HDL Cholesterol - Triglycerides	6		rs13702-A (NR)	HDL Cholesterol - Triglycerides	Atherosclerosis; Bursitis; Cystic fibrosis; Diabetes, Type 2; Diabetes, general; Diabetic complication, general; Hypercholesterolaemia; Hyperlipidaemia, general; Infarction, myocardial; Infection, herpes simplex virus; Inflammation, vascular; Nephropathy, diabetic; Pancreatic dysfunction, general; Retinopathy, diabetic; Steatohepatitis; Thrombosis, general; Venous insufficiency	Vessiflex; Alipogene tiparvovec; Bezafibrate; Binifibrate; Ciprofibrate; Docosanil; Eniclobrate; Etofibrate; Gemfibrozil; Pancreatin, Solvay; Sulodexide, Alfa Wassermann; Sulodexide, Ker
LPL	lipoprotein lipase	Triglycerides- Blood Pressure	6		rs15285-A (NR)	Triglycerides- Blood Pressure	Atherosclerosis; Bursitis; Cystic fibrosis; Diabetes, Type 2; Diabetes, general; Diabetic complication, general; Hypercholesterolaemia; Hyperlipidaemia, general; Infarction, myocardial; Infection, herpes simplex virus; Inflammation, vascular; Nephropathy, diabetic; Pancreatic dysfunction, general; Retinopathy, diabetic; Steatohepatitis; Thrombosis, general; Venous insufficiency	Vessiflex; Alipogene tiparvovec; Bezafibrate; Binifibrate; Ciprofibrate; Docosanil; Eniclobrate; Etofibrate; Gemfibrozil; Pancreatin, Solvay; Sulodexide, Alfa Wassermann; Sulodexide, Ker
LPL	lipoprotein lipase	Hypertriglycer idemia	5		rs7016880-? (0.90)	Hypertriglycerid emia	Atherosclerosis; Bursitis; Cystic fibrosis; Diabetes, Type 2; Diabetes, general; Diabetic complication, general; Hypercholesterolaemia; Hyperlipidaemia, general; Infarction, myocardial; Infection, herpes simplex virus; Inflammation, vascular; Nephropathy, diabetic; Pancreatic dysfunction, general; Retinopathy, diabetic; Steatohepatitis; Thrombosis, general; Venous insufficiency	Vessiflex; Alipogene tiparvovec; Bezafibrate; Binifibrate; Ciprofibrate; Docosanil; Eniclobrate; Etofibrate; Gemfibrozil; Pancreatin, Solvay; Sulodexide, Alfa Wassermann; Sulodexide, Ker
LRP1	low density lipoprotein receptor-related protein 1	Migraine	7		rs11172113-T (0.59)	Migraine	Cancer, liver; Infection, hepatitis virus, unspecified; Not applicable	HepTide; Antiviral, HepTide; Doxorubicin, HepTi
LRRK2	leucine-rich repeat kinase 2	Crohn's disease	83		rs11175593-T (0.02), rs11564258-A (0.03)	Crohn's disease	Alzheimer's disease; Cancer, general; Parkinson's disease	LRRK2 inhibitors, Vernalis; LRRK2 inhibitors, Zenobia; TTT-30

Table 1		Strongest			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)			
LRRK2	leucine-rich repeat kinase 2	Parkinson's disease	47	rs1491942-G (0.08), rs1994090-? (NR)	Parkinson's disease	Alzheimer's disease; Cancer, general; Parkinson's disease	LRRK2 inhibitors, Vernalis; LRRK2 inhibitors, Zenobia; TTT-30
LTA	lymphotoxin alpha (TNF superfamily, member 1)	Neonatal lupus	10	rs3099844-? (0.11)	Neonatal lupus	Arthritis, rheumatoid; Cancer, oesophageal	53550; RG-7416; Recombinant human lymphotoxin-alpha derivative, Fudan-Zhangjia
LY75	lymphocyte antigen 75	Nephropathy	23	rs4664308-? (0.43)	Nephropathy	Cancer, bladder; Cancer, breast; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, sarcoma, osteo; Cancer, solid, general; Infection, HIV prophylaxis; Infection, HIV/AIDS	CDX-1401; CDX-24
MAPT	microtubule-associated protein tau	Parkinson's disease	47	rs11012-T (NR), rs199533-C (0.78), rs2942168-G (0.78), rs393152-A (0.82), rs8070723-? (0.76)	Parkinson's disease	Alzheimer's disease; Cancer, general; Diagnosis, CNS; Parkinson's disease	Alzheimer's MAb, AC Immune-2; Alzheimer's disease therapy, TauRx; Alzheimer's disease therapy, Treventis; Alzheimer's imaging agent, Avid; Alzheimer's therapy, Oligomerix; BLV-0703; LMT-X; ReS10-T; ReS19-T; ReS3-T; ReS8-T; TTT-3002; Methylnitrothionium chloride, TauRx; Tau vaccine, AC Immu
MC1R	melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor)	Melanoma	4	rs258322-A (0.09), rs4785763-A (0.32)	Melanoma	Acne; Albinism; Arthritis, rheumatoid; Cancer, melanoma; Cancer, squamous cell; Diabetes, Type 2; Eczema, atopic; Erythropoietic protoporphyria; Inflammatory bowel disease, general; Insulin-related metabolic syndrome; Keratosis, actinic; Obesity; Photodamage; Polymorphous light eruption; Psoriasis; Renal failure; Respiratory distress syndrome, adult; Urticaria; Uveitis; Vitiligo	AP-1030; AP-1189; AP-214; AP-405; JNJ-10229570; ME-10393; MSH fusion toxin; Afamelanotide; DRI-alpha-MSH, Sano

Table 1					All drugs		
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	
MET	met proto-oncogene (hepatocyte growth factor receptor)	Multiple sclerosis	59	rs10243024-? (0.23)	Multiple sclerosis	Acute lung injury; Cancer, biliary; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, cervical; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, stomach; Cancer, head and neck; Cancer, liver; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, neuroendocrine, Merkel cell carcinoma; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, general; Cancer, oesophageal; Cancer, oral; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, glial; Cancer, sarcoma, lipo; Cancer, sarcoma, soft tissue; Cancer, solid, general; Cancer, squamous cell; Cancer, testicular; Cancer, thyroid; Cancer, vaginal; Fibrosis, liver; Heart failure; Infarction, myocardial; Renal failure; Spinal cord injury; Transplant rejection, general; Ulcer, general; Wound healing	BAY-85-3474; BB-3; HuMax-cMet; INCB-028060; JNJ-38877605; LY-2875358; MGCD-265; PF-4217903; Cabozantinib; Crizotinib; Ficlatusumab; Foretinib; Golvatinib; Hepatocyte growth factor, ChronoTech Pharma; Onartuzumab; Rilotumumab; Tivantin
MTNR1A	melatonin receptor 1A	Obesity	29	rs925642-? (NR)	Obesity	Addiction, tranquilizer; Alzheimer's disease; Apnoea; Depression, general; Depression, major depressive disorder; Dyskinesia, tardive; Generalized anxiety disorder; Insomnia; Migraine prophylaxis; Obsessive-compulsive disorder; Sleep disorder, general	GW-290569; NCT-600; SL-18.1616; Agomelatine; Buspirone + melatonin, BrainCells; Melatonin, Neurim; Ramelteon; Tasimelte
MTNR1B	melatonin receptor 1B	Fasting plasma glucose	6	rs10830963-G (0.28), rs1387153-T (0.29), rs2166706-G (0.46)	Fasting plasma glucose	Addiction, tranquilizer; Alzheimer's disease; Apnoea; Depression, general; Depression, major depressive disorder; Dyskinesia, tardive; Generalized anxiety disorder; Insomnia; Migraine prophylaxis; Obsessive-compulsive disorder; Sleep disorder, general	GW-290569; NCT-600; SL-18.1616; Agomelatine; Buspirone + melatonin, BrainCells; Melatonin, Neurim; Ramelteon; Tasimelte

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
MTNR1B	melatonin receptor 1B	Type 2 diabetes	61	rs1387153-T (NR)	Type 2 diabetes	Addiction, tranquilizer; Alzheimer's disease; Apnoea; Depression, general; Depression, major depressive disorder; Dyskinesia, tardive; Generalized anxiety disorder; Insomnia; Migraine prophylaxis; Obsessive-compulsive disorder; Sleep disorder, general	GW-290569; NCT-600; SL-18.1616; Agomelatine; Buspirone + melatonin, BrainCells; Melatonin, Neurim; Ramelteon; Tasimelte
MTNR1B	melatonin receptor 1B	Fasting glucose-related traits	18	rs10830963-G (0.30)	Fasting glucose-related traits	Addiction, tranquilizer; Alzheimer's disease; Apnoea; Depression, general; Depression, major depressive disorder; Dyskinesia, tardive; Generalized anxiety disorder; Insomnia; Migraine prophylaxis; Obsessive-compulsive disorder; Sleep disorder, general	GW-290569; NCT-600; SL-18.1616; Agomelatine; Buspirone + melatonin, BrainCells; Melatonin, Neurim; Ramelteon; Tasimelte
MUC1	mucin 1, cell surface associated	Crohn's disease	83	rs3180018-A (0.25)	Crohn's disease	Cancer, bladder; Cancer, breast; Cancer, colorectal; Cancer, fallopian tube; Cancer, gastrointestinal, general; Cancer, general; Cancer, head and neck; Cancer, liver; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, myeloma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, solid, general; Diagnosis, cancer	AS-109; AS-1402; AS-1403; Brevax MAb; CMB-401; CVac; GO-203-2c; GT-MAB 2.5-GEX; R-1549; SAR-56658; TG-4010; Emepepimut-S; Falimarev + inalimarev; HPAM4-SN-38; ImMucin; Mannan-MUC1, Viralytics; Yttrium Y 90 clivatuzumab tetraxet
MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	Ovarian cancer	10	rs10088218-G (NR)	Ovarian cancer	Cancer, breast; Cancer, general; Cancer, head and neck; Cancer, prostate; Polycystic kidney disease; Restenosis	AVI-4126; INXC-6295; Degrasyl
NAGLU	N-acetylglucosaminidase, alpha	Conduct disorder	17	rs7581919-? (0.041)	Conduct disorder	Mucopolysaccharidosis IIIB	623
NCAM1	neural cell adhesion molecule 1	Left ventricular mass	3	rs1436109-? (NR)	Left ventricular mass	Alzheimer's disease; Cancer, brain; Cancer, cervical; Cancer, gastrointestinal, general; Cancer, lung, small cell; Cancer, myeloma; Cancer, neuroendocrine, Merkel cell carcinoma; Cancer, neuroendocrine, general; Cancer, ovarian; Cancer, sarcoma, general; Cancer, skin, general; Cancer, solid, general; Cognitive disorder, unspecified; Spinal cord injury	EMD-56700; ERIC-1; PR-21, Pharmaxon; HuN901-DC1; Lorvotuzumab mertansi

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
NEDD4	neural precursor cell expressed, developmentally down-regulated 4	Keloid	2	rs8032158-C (0.36)	Keloid	Infection, influenza virus prophylaxis
NEDD4	neural precursor cell expressed, developmentally down-regulated 4	Chronic lymphocytic leukemia	17	rs7169431-A (NR)	Chronic lymphocytic leukemia	Infection, influenza virus prophylaxis

All drugs

FGI-1

FGI-1

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes					
NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B- cells 1	Primary biliary cirrhosis	26	rs7665090-C (0.52)	Primary biliary cirrhosis	Acute coronary syndrome; Amyloidosis; Arthritis, osteo; Arthritis, rheumatoid; Asthma; Cancer, biliary; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, gastrointestinal, general; Cancer, head and neck; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, chronic myelogenous; Cancer, liver; Cancer, lung, non- small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, neuroendocrine, carcinoid; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, osteo; Cancer, sarcoma, soft tissue; Cancer, solid, general; Cancer, thyroid; Chronic obstructive pulmonary disease; Colitis, ulcerative; Diabetes, Type 2; Eczema, atopic; Glaucoma; Glomerulonephritis; Hepatitis, non-infectious; Inflammation, general; Inflammatory bowel disease, general; Ischaemia, cerebral; Mucositis, general; Myelodysplastic syndrome; Nephropathy, diabetic; Pain, general; Pain, neuropathic; Parkinson's disease; Psoriasis; Regeneration, cartilage; Renal failure; Restenosis; Transplant rejection, bone marrow; Waldenstrom's hypergammaglobulinaemia	7-Hydroxyfrullanolide, Piramal; ALT-2074; HE-3286; MLN-9708; Nfkb decoy gene ther, Dainippon; Nfkb decoy oligo, AnGes; OT-440; P-1639; Bardoxolone; Bardoxolone methyl; Bortezomib; Declopramide; Quinacrine, Cleveland; Tarenflurbil, PAZ; Teglarinad chlori	
NOS2	nitric oxide synthase 2, inducible	Psoriasis	30	rs4795067-G (0.35)	Psoriasis	Arthritis, osteo; Arthritis, rheumatoid; Head trauma; Hypotension; Inflammatory bowel disease, general; Ischaemia, cerebral; Migraine; Mucositis, general; Pain, general; Pain, neuropathic; Radio/chemotherapy- induced injury, GI; Radio/chemotherapy- induced mucositis; Restenosis; Sepsis	CR-3294; KD-7332; KLYP-956; PMI-005; SD-6010; VAS- 203; INOS gene therapy, GenVec; NNOS/iNOS inhibitors, NeurAxon; Targini	

Table 1							
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
NR4A2	nuclear receptor subfamily 4, group A, member 2	Response to statin therapy	75	rs16839962-T (0.13)	Response to statin therapy	Parkinson's disease	Nurr1-RXR agonists, ACAD
NRG1	neuregulin 1	Dialysis-related mortality	31	rs2439312-? (0.24)	Dialysis-related mortality	Heart failure; Multiple sclerosis, general	Glial growth factor-2, Paion; RhNRG
NRG1	neuregulin 1	Hirschsprung's disease	4	rs16879552-G (0.61)	Hirschsprung's disease	Heart failure; Multiple sclerosis, general	Glial growth factor-2, Paion; RhNRG
NRG1	neuregulin 1	Hip geometry	7	rs10503887-? (NR)	Hip geometry	Heart failure; Multiple sclerosis, general	Glial growth factor-2, Paion; RhNRG
NRP1	neuropilin 1	Schizophrenia	33	rs1412115-? (0.37)	Schizophrenia	Cancer, ovarian; Cancer, prostate; Cancer, solid, general	MNRP-1685A; RG-73

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
OPRM1	opioid receptor, mu 1	Coronary heart disease	78	rs675026-? (0.72)
				Coronary heart disease
				Addiction, alcohol; Addiction, cocaine; Addiction, drug, unspecified; Addiction, gambling; Addiction, narcotic/opiate; Addiction, nicotine; Anaesthesia, adjunct; Binge eating disorder; Bulimia; Cancer, lung, non-small cell; Constipation; Depression, general; Depression, major depressive disorder; Dyskinesia, levodopa-induced; Ileus; Infarction, myocardial; Irritable bowel syndrome; Migraine; Motility dysfunction, GI, general; Nausea and vomiting, opiate-induced; Neuropathy, diabetic; Obesity; Pain, cancer; Pain, general; Pain, musculoskeletal, arthritis; Pain, musculoskeletal, general; Pain, neuropathic; Pain, post-herpetic; Pain, post-operative; Poisoning, drug; Premature ejaculation; Pruritus; Restless legs syndrome; Rhinitis, allergic, general; Rhinitis, general; Sepsis; Urinary retention
				Current indications
				New suggested indication
				All drugs
				57138; 58209; 59760; 9624; ADL-5510; ADL-5945; ADL-7445; ALKS-33; ALKS-36; ALKS-5461; Cyt-1010; DPI-3290; EP-94; GSK-1521498; HydrocoDex; JNJ-27018966; KIN-3031; KIN-4044; LY-255582; NCT-400; NKP-206; NKTR-119; NKTR-181; NRP-290; NRT-300; PTI-609; Penntuss; PercoDex; SYN-1003; TD-1211; Acetaminophen + hydrocodone, Qu; Acetaminophen + propoxyphene, Xanodyne; Acetaminophen + tramadol, Ethypharm; Alfentanil; Alvimopan; Buprenorphine; Buprenorphine + naloxone; Buprenorphine + naloxone, Aoxing; Buprenorphine + naloxone, BDI; Buprenorphine + naloxone, Nanotherapeutics; Buprenorphine + naloxone, Orexo; Buprenorphine, BEMA film (low dose); Buprenorphine, Camurus; Buprenorphine, Elbion; Buprenorphine, Encore; Buprenorphine, Gruenthal; Buprenorphine, Labtec; Buprenorphine, Mundipharma; Buprenorphine, ProNeura; Buprenorphine, Vernalis; Buprenorphine, Vyteris; Buprenorphine, sublingual; Bupropion + naltrexone, Orexigen; Butorphanol tartrate; Butorphanol, MDRNA; Chiral methadones, SAF; Dextetoprofen trometamol + tramadol hydrochloride, Menarini; Dextropropoxyphene, Benzon; Dihydrocodeine, Mundipharma; Fentanyl (sublingual), INSYS; Fentanyl citrate, Altea; Fentanyl citrate, Anesta; Fentanyl citrate, Glide; Fentanyl citrate, Hisamitsu; Fentanyl citrate, Orexo; Fentanyl film, Auxilium; Fentanyl patch, Nippon Kayaku; Fentanyl, Acrux; Fentanyl, Alexza; Fentanyl, Alza; Fentanyl, Archimedes; Fentanyl, BioAlliance Pharma; Fentanyl, CIMA; Fentanyl, DELEX; Fentanyl, E-TRANS; Fentanyl, Ethypharm; Fentanyl, Lavipharm; Fentanyl, Meda; Fentanyl, NAL Pharma-3; Fentanyl, Taifun; Fentanyl, Watson; Fentanyl, nasal, Nycomed;

Table 1					Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associate d genes					
OPRM1 continued	opioid receptor, mu 1	Coronary heart disease	78	rs675026-? (0.72)	Coronary heart disease	Addiction, alcohol; Addiction, cocaine; Addiction, drug, unspecified; Addiction, gambling; Addiction, narcotic/opiate; Addiction, nicotine; Anaesthesia; adjunct; Binge eating disorder; Bulimia; Cancer, lung, non-small cell; Constipation; Depression, general; Depression, major depressive disorder; Dyskinesia, levodopa-induced; Ileus; Infarction, myocardial; Irritable bowel syndrome; Migraine; Motility dysfunction, GI, general; Nausea and vomiting, opiate-induced; Neuropathy, diabetic; Obesity; Pain, cancer; Pain, general; Pain, musculoskeletal, arthritis; Pain, musculoskeletal, general; Pain, neuropathic; Pain, post-herpetic; Pain, post- operative; Poisoning, drug; Premature ejaculation; Pruritus; Restless legs syndrome; Rhinitis, allergic, general; Rhinitis, general; Sepsis; Urinary retention	Fentanyl, transdermal, Dr Reddy's; Fluoxetine + naltrexone, Orex; Flupirtine + opioid, CNSBio; Hydrocodone + acetaminophen + niacin, Acura; Hydrocodone + acetaminophen, Abbott; Hydrocodone + ibuprofen,ProEth; Hydrocodone + ibuprofen,Watson; Hydrocodone + naltrexone, King; Hydrocodone + promethazine + acetaminophen; Hydrocodone bitartrate, Cephalon; Hydrocodone+acetaminophen, Vic; Hydrocodone, Egalet; Hydrocodone, Egalet-2; Hydrocodone, Inspirion Delivery Technologies; Hydromorphone HCl, OROS; Hydromorphone, CR, Egalet; Hydromorphone, Inspirion Delivery Technologies; Hydromorphone, Napp; Ibuprofen (CR) + codeine, Napp; Ibuprofen + hydrocodone,Abbott; Ibuprofen combination, Adcock; Levorphanol, TheraQuest; Methylnaltrexone, Progenics; Mirfentanil; Morphine + naltrexone, Alpharma; Morphine + oxycodone, QRx (oral); Morphine + oxycodone, QRx-2; Morphine +oxycodone, QRx (iv); Morphine SR, Takeda; Morphine sulfate, aaiPharma; Morphine, DepoFoam; Morphine, Egalet; Morphine, Elan; Morphine, Ethypharm; Morphine, Hospira; Morphine, Inspirion Delivery Technologies; Morphine, Javelin; Morphine, Karo Bio; Morphine, Nycomed Amersham; Morphine, Paion; Morphine, Rhotard; Morphine, Takeda; Morphine, Wyeth; Morphine-6-glucuronide, Paion; Mu opioid, iv, Trevena; Mu opioid, oral, Trevena; Nalbuphine; Nalbuphine, nasal; Nalmefene; Nalmefene, BioTie; Naloxol, Nektar; Naloxone, Bristol-Myers Squibb; Naloxone, Cosmo; Naloxone, Lightlake Therapeutics; Naloxone, SLA Pharma; Naloxone, lotion, Elorac; Naloxone, sublingual film, Aoxing; Naltrexone; Naltrexone, Alkermes; Naltrexone, Pain Ther; Oxycodone (iv), Napp; Oxycodone + acetaminophen + niacin, Acura;	

Table 1		Strongest			New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)						
OPRM1 continued	opioid receptor, mu 1	Coronary heart disease	78	rs675026-? (0.72)	Coronary heart disease		Addiction, alcohol; Addiction, cocaine; Addiction, drug, unspecified; Addiction, gambling; Addiction, narcotic/opiate; Addiction, nicotine; Anaesthesia, adjunct; Binge eating disorder; Bulimia; Cancer, lung, non-small cell; Constipation; Depression, general; Depression, major depressive disorder; Dyskinesia, levodopa-induced; Ileus; Infarction, myocardial; Irritable bowel syndrome; Migraine; Motility dysfunction, GI, general; Nausea and vomiting, opiate-induced; Neuropathy, diabetic; Obesity; Pain, cancer; Pain, general; Pain, musculoskeletal, arthritis; Pain, musculoskeletal, general; Pain, neuropathic; Pain, post-herpetic; Pain, post-operative; Poisoning, drug; Premature ejaculation; Pruritus; Restless legs syndrome; Rhinitis, allergic, general; Rhinitis, general; Sepsis; Urinary retention		Oxycodone + acetaminophen, Labopharm; Oxycodone + ibuprofen, BTG; Oxycodone + naloxone, Purdue; Oxycodone + naltrexone, Elite; Oxycodone + naltrexone, Pain T; Oxycodone + niacin, Acura; Oxycodone + paracetamol, Covid; Oxycodone hydrochloride, Xano; Oxycodone patch, Phosphagenics; Oxycodone+dextromethorphan, Oxycodone+naltrexone, Alpharma; Oxycodone, Acura; Oxycodone, CR, Egalet; Oxycodone, Collegium; Oxycodone, Elite, CR; Oxycodone, IntelliPharmaCeutics; Oxycodone, Purdue Pharma; Oxycodone, extended-release, Inspiron Delivery Technologies; Oxycodone, long-acting, Pain T; Oxymorphone ER, crush-resistant; Oxymorphone, Endo-2; Oxymorphone, Inspiron Delivery Technologies; Oxymorphone, Pain Therapeutics; Oxymorphone, TIMERx; Paracetamol + codeine, Alza; Paracetamol+dihydrocodeine, Na; Remifentanyl; Remifentanyl, Vyteris; Sameridine; Sufentanil; Sufentanil+triazolam, AcelRx; Sufentanil, Labtec; Sufentanil, TRANSDUR; Sufentanil, sublingual, AcelRx; Sufentanil, sublingual, AcelRx-2; Sufentanil, sublingual, AcelRx-3; Tapentadol, ER; Tapentadol, IR; Tilidine + naloxone, Aoxing Pharmaceutical; Tilidine hydrochloride, Aoxing Pharmaceutical; Tramadol; Tramadol + NSAID, Biovai; Tramadol hydrochloride + erectile dysfunction therapy; Tramadol hydrochloride, Ampio Pharmaceuticals; Tramadol, Ciph	
OSM	oncostatin M	Nephropathy	23	rs2412971-? (0.49 (EA))	Nephropathy		Arthritis, rheumatoid		3152	
PCSK9	proprotein convertase subtilisin/kexin type 9	Coronary heart disease	78	rs11206510-T (0.82)	Coronary heart disease		Atherosclerosis; Hypercholesterolaemia; Hyperlipidaemia, general		ALN-PCS; AMG-145; BMS-844421; BMS-PCSK9Rx-2; LDL-4X4; PCSK9 Adnectin, Bristol-Myers Squibb; PCSK9 siRNA drug signal, Nativis; REGN-727; REGN-728; RN-316; SPC-50	

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
PDE10A	phosphodiesterase 10A	Conduct disorder	17	rs7762160-? (0.365)	Conduct disorder	Addiction, narcotic/opiate; Alzheimer's disease; Asthma; Conjunctivitis, inflammatory; Infarction, cerebral; Insulin-related metabolic syndrome; Multiple sclerosis, general; Neuropathy, diabetic; Pain, chemotherapy-induced; Pain, neuropathic; Psychosis, bipolar; Psychosis, general; Schizophrenia
PDE2A	phosphodiesterase 2A, cGMP-stimulated	Optic disc size	17	rs12418204-G (NR)	Optic disc size	Adenoma, colorectal; Alzheimer's disease; Barrett's oesophagus; Cancer, bladder; Cancer, breast; Cancer, leukaemia, chronic lymphocytic; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, prostate; Cancer, renal; Crohn's disease; Inflammatory bowel disease, general
PDE3A	phosphodiesterase 3A, cGMP-inhibited	Male infertility	5	rs10841496-? (0.58)	Male infertility	Asthma; Atherosclerosis; Buerger's syndrome; Chronic obstructive pulmonary disease; Diabetic complication, general; Heart failure; Infarction, cerebral; Inflammation, urinary tract; Peripheral vascular disease; Polycythaemia vera; Rhinitis, allergic, seasonal; Thrombocythaemia; Thrombocytosis
						All drugs
						8045; EVP-6308; EVX-001650; PDE 10 inhibitors, Omeros; PDE-10 inhibitor, Biocrea; PDE-2/10 inhibitor, Biocrea; PDE-Xa inhibitors, Evotec; PF-2545920; Ibudilast; Phosphodiesterase X inhibitor, Lundbe
						CEL-031; PDE-2/10 inhibitor, Biocrea; Exisuli
						CR-3465; RPL-554; Amrinone; Anagrelide hydrochloride; Cilostazol; Enoximone; Loprinone hydrochloride; Milrinone; Oberadilol; Parogreil hydrochloride; Pumafentrine; Tipeluka

Table 1		Strongest				New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)							
PDE4D	phosphodiesterase 4D, cAMP-specific	Esophageal cancer	15	rs10052657-C (0.78)	Esophageal cancer	Addiction, narcotic/opiate; Alzheimer's disease; Ankylosing spondylitis; Anxiety, general; Arthritis, general; Arthritis, psoriatic; Arthritis, rheumatoid; Asthma; Behcet's disease; Chronic obstructive pulmonary disease; Cognitive disorder, unspecified; Colitis, ulcerative; Conjunctivitis, inflammatory; Crohn's disease; Depression, major depressive disorder; Eczema, atopic; Eczema, contact; Heart failure; Infarction, cerebral; Infarction, myocardial; Inflammation, general; Inflammatory bowel disease, general; Ischaemia, cerebral; Lupus erythematosus, cutaneous; Multiple sclerosis, general; Multiple sclerosis, relapsing-remitting; Neuropathy, diabetic; Pain, chemotherapy-induced; Pain, general; Pain, musculoskeletal, arthritis; Pain, neuropathic; Pruritus; Psoriasis; Reperfusion injury; Respiratory disease, general; Rhinitis, allergic, general; Rhinitis, allergic, seasonal; Sarcoidosis; Steatohepatitis; Thrombosis, general				8045; AN-2728; AN-2898; ASP-9831; CC-10015; CC-11050; COPD therapy, Spring Bank; D-22888; DE-103; DG-071; DWP-205297; GSK-256066; GSK-356278; GW-3600; IPL-455903; KW-4490; LAS-37779; OX-914; RPL-554; RPR-122818 derivatives; RPR-132294; TA-7906; TPI-1100; V-11294A; Apremilast; Filaminast; Fosfosal; Ibudilast; Loprinone hydrochloride; Mesopram; Oglemilast; Roflumilast; Ronomilast; Simvastatin + triflusal stent; Tetomilast; Tipelukast; Triflus	
PDX1	pancreatic and duodenal homeobox 1	Attention deficit hyperactivity disorder and conduct disorder	30	rs9512900-C (0.37)	Attention deficit hyperactivity disorder and conduct disorder	Cancer, neuroendocrine, pancreatic; Cancer, pancreatic				Pbi-shPDX-1 LP, Gradal	
PIM3	pim-3 oncogene	Ulcerative colitis	96	rs5771069-G (0.51)	Ulcerative colitis	Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, general; Cancer, lymphoma, non-Hodgkin's; Cancer, pancreatic; Cancer, prostate				CX-6258; SGI-1776; Pim kinase inhibitors, Jas	
PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-dependent)	Knee osteoarthritis	6	rs4140564-? (0.05)	Knee osteoarthritis	Arthritis, rheumatoid; Glomerulonephritis; Psoriasis				AVX-001; AVX-002; AVX-0	

Table 1

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	All drugs	
					New suggested indication	Current indications
POMC	proopiomelanocortin	Body mass index	70	rs713586-C (0.47)	Body mass index	Poisoning, metal Melanotropin alpha, Mondobiotec
PPARδ	peroxisome proliferator-activated receptor delta	Response to antipsychotic treatment	18	rs9658108-? (0.052)	Response to antipsychotic treatment	Atherosclerosis; Diabetes, Type 2; Hypercholesterolaemia; Hyperlipidaemia, general; Hypertriglyceridaemia; Insulin-related metabolic syndrome; Multiple sclerosis, general; Obesity CER-002; DB-959; HPP-593; MBX-8025; NN-0606; PPAR pan-agonists, Plexikon-3; PPAR-alpha/delta agonists, Genfit; PPAR-delta agonist, Nippon-2; Multiple sclerosis therapy, Plexxik
PRKCE	protein kinase C, epsilon	Hemoglobin	7	rs10495928-G (NR)	Hemoglobin	Arthritis, rheumatoid; Diabetes, Type 2; Hyperuricaemia; Obesity; Pain, neuropathic; Pain, post-herpetic; Pain, post-operative; Psoriasis; Transplant rejection, general; Uveitis CDE-6960; KAI-1678; PN-2034; Sotrastaur
PRKCG	protein kinase C, theta	Type 1 diabetes	50	rs11258747-? (NR), rs947474-G (0.19)	Type 1 diabetes	Arthritis, rheumatoid; Multiple sclerosis, general; Psoriasis; Transplant rejection, bone marrow; Transplant rejection, general; Uveitis CDE-6960; R-057; R-461; Sotrastaur
PRNP	prion protein	Creutzfeldt-Jakob disease	2	rs1799990-A (NR)	Creutzfeldt-Jakob disease	Alzheimer's disease Cognition enhancers, Axerion Therapeuti
PTGER4	prostaglandin E receptor 4 (subtype EP4)	Ulcerative colitis	96	rs6451493-T (0.61)	Ulcerative colitis	Allergy, general; Arthritis, osteo; Bone disorder, general; Inflammation, general; Migraine; Pain, general; Pain, musculoskeletal, arthritis; Pain, musculoskeletal, general BGC20-1531; CJ-23423; CR-5790; MF-592; PGN-9863; RQ-7; RQ-8; Anti-inflammatory, Merck &
PTGER4	prostaglandin E receptor 4 (subtype EP4)	Multiple sclerosis	59	rs6896969-C (0.62)	Multiple sclerosis	Allergy, general; Arthritis, osteo; Bone disorder, general; Inflammation, general; Migraine; Pain, general; Pain, musculoskeletal, arthritis; Pain, musculoskeletal, general BGC20-1531; CJ-23423; CR-5790; MF-592; PGN-9863; RQ-7; RQ-8; Anti-inflammatory, Merck &
PTK2	PTK2 protein tyrosine kinase 2	Response to interferon beta therapy	4	rs4961252-G (0.40)	Response to interferon beta therapy	Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, head and neck; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, lymphoma, non-Hodgkin's; Cancer, neuroendocrine, general; Cancer, neuroendocrine, neuroblastoma; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, solid, general; Cancer, squamous cell CEP-37440; CFAK-C4; CFAK-Y15; GSK-2256098; PF-04554878; PF-5622

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes							
PTPN11	protein tyrosine phosphatase, non-receptor type 11	Type 1 diabetes	50	rs6679677-A (0.10)	Type 1 diabetes		Cancer, colorectal; Cancer, head and neck; Cancer, leukaemia, general; Cancer, melanoma; Cancer, mesothelioma; Cancer, neuroendocrine, general; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, solid, general; Cancer, squamous cell; Infection, leishmaniasis; Nerve injury, general; Neuropathy, diabetic		AEG-19915; Sodium stibogluconate, VioQue	
PTPN11	protein tyrosine phosphatase, non-receptor type 11	Retinal vascular caliber	18	rs10774625-A (0.48)	Retinal vascular caliber		Cancer, colorectal; Cancer, head and neck; Cancer, leukaemia, general; Cancer, melanoma; Cancer, mesothelioma; Cancer, neuroendocrine, general; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, solid, general; Cancer, squamous cell; Infection, leishmaniasis; Nerve injury, general; Neuropathy, diabetic		AEG-19915; Sodium stibogluconate, VioQue	
RAF1	v-raf-1 murine leukemia viral oncogene homolog 1	Cardiac hypertrophy	22	rs3729931-? (NR)	Cardiac hypertrophy		Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, general; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, neuroendocrine, carcinoid; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, solid, general; Cancer, thyroid; Infection, hepatitis-C virus; Macular degeneration, age-related, wet; Myelodysplastic syndrome; Oedema, macular, diabetic; Pain, general; Pain, neuropathic; Polycystic kidney disease; Retinopathy, diabetic		BIB-024; DP-2874; Debio-0928; ISIS-5132; LÉrafAON-ETU; PLX-5568; Pharmaprojects No. 6222; RG-7304; RO-5126766; SAR-397769; STP-503; XL-281; ICo-007; Sorafen	

Table 1		Strongest SNP-Risk Allele (frequency)				New suggested indication		Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes								
RARB	retinoic acid receptor, beta	Obesity	29	rs1435703-T (0.06)		Obesity		Acne; Cancer, general; Cancer, leukaemia, acute myelogenous; Cancer, liver; Cancer, lung, non-small cell; Cancer, myeloma; Crohn's disease; Multiple sclerosis, general; Psoriasis; Wound healing		Epiduo; Adapalene; Tamibarotene; Tazarotene; Tazarotene, or	
RET	ret proto-oncogene	Hirschsprung's disease	4	rs2742234-T (NR)		Hirschsprung's disease		Cancer, biliary; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, stomach; Cancer, gastrointestinal, stromal; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, T-cell; Cancer, lymphoma, general; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, general; Cancer, neuroendocrine, pancreatic; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, general; Cancer, sarcoma, glial; Cancer, solid, general; Cancer, thyroid; Idiopathic myelofibrosis; Myelodysplastic syndrome; Polycythaemia vera; Thrombocytopenia, general		DCC-2157; SAR-302503; Apatinib; Cabozantinib; Motesanib diphosphate; Regorafenib; Sorafenib; Sunitinib malate; Vandetan	
ROBO1	roundabout, axon guidance receptor, homolog 1 (Drosophila)	Brain imaging in schizophrenia	8	rs9836484-? (0.32)		Brain imaging in schizophrenia		Infection, HIV prophylaxis		FGI-1	
RORA	RAR-related orphan receptor A	Asthma	19	rs11071559-C (0.86)		Asthma		Cancer, leukaemia, acute lymphocytic		Anti-ROR-1 MABs, Kancera; Anticancer therapy, Kance	
RORA	RAR-related orphan receptor A	Response to citalopram treatment	5	rs809736-? (0.17)		Response to citalopram treatment		Cancer, leukaemia, acute lymphocytic		Anti-ROR-1 MABs, Kancera; Anticancer therapy, Kance	

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest		All drugs
				SNP-Risk Allele (frequency)	New suggested indication	
RORA	RAR-related orphan receptor A	Depression--quantitative trait	9	rs12912233-T (0.46)	Depression--quantitative trait	Cancer, leukaemia, acute lymphocytic
RTN4	reticulon 4	Obesity	29	rs6726292-G (0.73)	Obesity	Amyotrophic lateral sclerosis; Multiple sclerosis, general; Spinal cord injury
RXRG	retinoid X receptor, gamma	AIDS	3	rs10800098-A (0.05)	AIDS	Cancer, breast; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, lung, non-small cell; Cancer, lymphoma, T-cell; Cancer, ovarian; Cancer, renal; Cancer, sarcoma, Kaposi's; Diabetes, Type 2; Psoriasis
RYR2	ryanodine receptor 2 (cardiac)	Acute lymphoblastic leukemia	13	rs7554607-A (0.56)	Acute lymphoblastic leukemia	Arrhythmia, general; Heart failure
RYR2	ryanodine receptor 2 (cardiac)	Hypertension	22	rs2820037-T (0.14)	Hypertension	Arrhythmia, general; Heart failure
RYR2	ryanodine receptor 2 (cardiac)	Response to cerivastatin	1	rs2819742-G (0.62)	Response to cerivastatin	Arrhythmia, general; Heart failure
SCARB1	scavenger receptor class B, member 1	Renal cell carcinoma	2	rs4765623-? (0.34)	Renal cell carcinoma	Infection, hepatitis-C virus
SCN10A	sodium channel, voltage-gated, type X, alpha subunit	Atrioventricular conduction	6	rs6800541-C (0.41)	Atrioventricular conduction	Inflammation, general; Pain, cancer; Pain, general; Pain, neuropathic; Schizophrenia
SELL	selectin L	Amyotrophic lateral sclerosis	25	rs3177980-G (NR)	Amyotrophic lateral sclerosis	Acute lung injury; Anaemia, sickle cell; Asthma; Chronic obstructive pulmonary disease; Eczema, atopic; Epilepsy, general; Psoriasis; Respiratory distress syndrome, adult
SELPLG	selectin P ligand	Conduct disorder	17	rs8179116-? (0.021)	Conduct disorder	Psoriasis
SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporters), member 2	Brain imaging in schizophrenia	8	rs245201-? (0.32)	Brain imaging in schizophrenia	Hypertension, general; Ocular disorder, unspecified; Oedema, cardiac; Oedema, general
						Bumetanide; Ethacrynic acid, Telor; Furosemide AcuForm, Depomed; Piretanide; Torasemide; Torasemide ER, Penwest; Torasemide PR, Ferr

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporters), member 2	Ileal carcinoids	4	rs10089-? (NR)	Ileal carcinoids	Hypertension, general; Ocular disorder, unspecified; Oedema, cardiac; Oedema, general
SLC12A3	solute carrier family 12 (sodium/chloride transporters), member 3	HDL cholesterol	37	rs1800775-A (0.49)	HDL cholesterol	Hypertension, general
SLC6A1	solute carrier family 6 (neurotransmitter transporter, GABA), member 1	Conduct disorder	17	rs9990174-T (0.33)	Conduct disorder	Anxiety, general; Epilepsy, general

All drugs

Bumetanide; Ethacrynic acid, Telor; Furosemide
 AcuForm, Depomed; Piretanide; Torasemide;
 Torasemide ER, Penwest; Torasemide PR, Ferr

Acebutolol + HCTZ; Aliskiren + HCTZ, Novartis;
 Aliskiren + amlodipine + HCTZ, Novartis; Amlodipine +
 losartan + HCTZ, Merck; Amlodipine + losartan +
 hydrochlorothiazide, Hanmi;
 Amlodipine+HCTZ+valsartan, Nov; Atenolol +
 bendroflumethiazide; Atenolol + chlorthalidone;
 Azilsartan medoxomil + chlorthalidone; Benazepril +
 HCTZ; Bisoprolol fumarate + HCTZ;
 Bisoprolol+trichloromethiazide; Candesartan cilexetil +
 HCTZ; Delapril + indapamide, Chiesi; Enalapril maleate
 + HCTZ; Eprosartan mesylate + HCTZ; Indapamide;
 Indapamide, Douglas; Indapamide, SR, Servier;
 Irbesartan + HCTZ; Losartan + HCTZ, BMS; Moexipril +
 HCTZ; Moxonidine + HCTZ, Abbott; Nebivolol +
 indapamide, Zydus Cadila; Olmesartan
 medoxomil+HCTZ, San; Perindopril + indapamide,
 Serv; Telmisartan + HCTZ; Valsartan + HC

Deramciclane fumarate; Tiagabi

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
SNCA	synuclein, alpha (non A4 component of amyloid precursor)	Parkinson's disease	47	rs11931074-? (NR), rs2736990-? (NR), rs2736990-C (0.51), rs356219-G (0.39), rs356220-A (0.36), rs356220-T (0.35), rs356220-T (0.36)	Parkinson's disease	Parkinson's disease
SOD1	superoxide dismutase 1, soluble	Amyotrophic lateral sclerosis	25	rs13048019-T (0.17)	Amyotrophic lateral sclerosis	Alzheimer's disease; Amyotrophic lateral sclerosis; Cardiomyopathy, ischaemic; Peyronie's disease; Radio/chemotherapy-induced eczema; Wound healing
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	Crohn's disease	83	rs744166-A (0.57)	Crohn's disease	Arthritis, rheumatoid; Cancer, breast; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, pancreatic; Cancer, renal; Cancer, solid, general; Cancer, thyroid; Hepatitis, non-infectious; Myelodysplastic syndrome; Nephropathy, diabetic; Renal failure
						All drugs
						PD-01, Affiris; Parkinson's therapy, FoldRx; ReS12-S; Synucle
						ALS MAb, Amorfix; ALS RNAi therapy, RXi; ALS vaccine, Amorfix; Alzheimer's Ab therapy, Amorfix; Alzheimer's vaccine, Amorfix; ISIS-333611; Superoxide dismutase, Polymun; Superoxide dismutase, U
						OPB-31121; OPB-51602; Bardoxolone methyl; Brivudine, RESprote

Table 1		Strongest			New suggested indication			Current indications		All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication			Current indications		All drugs	
STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)	Multiple sclerosis	59	rs744166-G (0.41)	Multiple sclerosis			Arthritis, rheumatoid; Cancer, breast; Cancer, leukaemia, acute lymphocytic; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic myelogenous; Cancer, leukaemia, general; Cancer, lung, non-small cell; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, myeloma; Cancer, ovarian; Cancer, pancreatic; Cancer, renal; Cancer, solid, general; Cancer, thyroid; Hepatitis, non-infectious; Myelodysplastic syndrome; Nephropathy, diabetic; Renal failure		OPB-31121; OPB-51602; Bardoxolone methyl; Brivudine, RESprote	
SUMF1	sulfatase modifying factor 1	Multiple sclerosis--Brain Glutamate Levels	5	rs794185-? (NR)	Multiple sclerosis--Brain Glutamate Levels			Mucopolysaccharidosis IIIA		Sulfamidase, Lysoge	
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Nephropathy	23	rs9357155-? (0.87 (EA))	Nephropathy			Cancer, breast		Breast cancer vaccine, TapImmu	
TERT	telomerase reverse transcriptase	Idiopathic pulmonary fibrosis	1	rs2736100-A (0.41)	Idiopathic pulmonary fibrosis			Anaemia, aplastic; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, general; Cancer, general; Cancer, leukaemia, acute myelogenous; Cancer, liver; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, solid, general; Cirrhosis, hepatic; Fibrosis, pulmonary; Myelodysplastic syndrome		51145; BSU-1021; CB-10-01; GV-1001; GX-301; Pharmaprojects No. 5840; TAT-153; TeloB-VAX; V934/V935; VX-001; Telomerase vaccine, Ger	
TH	tyrosine hydroxylase	Prostate cancer	30	rs7127900-A (0.20)	Prostate cancer			Parkinson's disease		ProSav	

Table 1		Strongest							
Gene	Description	GWAS phenotype	No. of associated genes	SNP-Risk Allele (frequency)	New suggested indication	Current indications	All drugs		
TLR7	toll-like receptor 7	Celiac disease	65	rs5979785-? (0.74)	Celiac disease	Arthritis, rheumatoid; Asthma; Atherosclerosis; Cancer, basal cell; Cancer, bladder; Cancer, melanoma; Cancer, skin, general; Cancer, solid, general; Infection, hepatitis-B virus; Infection, hepatitis-C virus; Infection, herpes simplex virus; Infection, human papilloma virus; Lupus erythematosus, general; Multiple sclerosis, general; Psoriasis; Rhinitis, allergic, general; Rhinitis, allergic, seasonal; Vaccine adjunct	12717; ANA-773; ANA-975; AZD-8848; DV-1179; GS-9620; IMO-3100; IPH-3201; TMX-201; VTX-463; Resiquimod; Vaccine adjuvants, TLR-7/8/9, Ide		
TLR8	toll-like receptor 8	Celiac disease	65	rs5979785-? (0.74)	Celiac disease	Arthritis, rheumatoid; Atherosclerosis; Cancer, lymphoma, B-cell; Cancer, lymphoma, general; Cancer, solid, general; Infection, hepatitis-C virus; Infection, herpes simplex virus; Lupus erythematosus, general; Multiple sclerosis, general; Psoriasis; Rhinitis, allergic, general; Vaccine adjunct	IMO-3100; IPH-3201; VTX-2337; VTX-463; Resiquimod; Vaccine adjuvants, TLR-7/8/9, Ide		

Table 1				
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)
TNF	tumor necrosis factor	Neonatal lupus	10	rs3099844-? (0.11)
				Neonatal lupus
				Alzheimer's disease; Amyloidosis; Anal fistula; Ankylosing spondylitis; Arthritis, general; Arthritis, juvenile; Arthritis, osteo; Arthritis, psoriatic; Arthritis, rheumatoid; Asthma; Behcet's disease; Cachexia; Cancer, biliary; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, gastrointestinal, stomach; Cancer, general; Cancer, head and neck; Cancer, lung, general; Cancer, lung, non-small cell; Cancer, melanoma; Cancer, myeloma; Cancer, oesophageal; Cancer, ovarian; Cancer, pancreatic; Cancer, prostate; Cancer, renal; Cancer, sarcoma, Kaposi's; Cancer, sarcoma, soft tissue; Cancer, solid, general; Cancer, thymoma; Cancer, thyroid; Cataract; Chronic obstructive pulmonary disease; Coeliac disease; Cognitive disorder, unspecified; Colitis, general; Colitis, ulcerative; Coronary artery bypass grafting; Crohn's disease; Diabetes, Type 1; Diabetes, Type 2; Diabetes, general; Eczema, atopic; Fibrosis, pulmonary, idiopathic; Heart failure; Hidradenitis suppurativa; Infarction, myocardial; Infection, HIV/AIDS; Infection, hepatitis-C virus; Infection, leprosy; Infection, malaria; Infection, unspecified; Inflammation, general; Inflammation, ocular; Inflammatory bowel disease, general; Ischaemia, cerebral; Lupus erythematosus, cutaneous; Macular degeneration, age-related, general; Multiple sclerosis, general; Myelodysplastic syndrome; Obesity; Pain, complex regional; Pain, musculoskeletal, general; Pain, neuropathic; Psoriasis; Radio/chemotherapy-induced mucositis;
				Current indications
				All drugs
				61687; AG-014; ALKS-6931; AME-527; ART-621; AVX-470; CEQ-600; CYT-020-TNFQb; ESBA-105; Humicade; ISIS-104838; ISIS-104838, oral; P-979-03; PD-2015; PD-2016; PD-2024; PF-05230905; Pharmaprojects No. 5357; Pharmaprojects No. 5534; SSS-07; Sphira; TNFQb; UR-1505; VGX-1027; VT-346; XPro-1595; YHB-1411-2; Adalimumab; Anti-TNF Ab, Protherics; Antidiabetic/antiobesity therapy, Avaxia; Arthritis therapy, NanoSmart-1; Certolizumab pegol; Etanercept; Etanercept, BioAssets Development; Etanercept, Cipla; Etanercept, Hanwha; Etanercept, LG Life Sciences; Etanercept, Lafrancol S.A.; Etanercept, Neurokine; Etanercept, Neurokine, liposomal; Etanercept, Protalix; Etanercept, Zenotech; Fibromun; Glycophosphopeptical, Cantabria; Golimumab; Golimumab, BioXpress; Golnerminogene pradenovec; Infliximab; Infliximab, BioXpress; Infliximab, Celltrion; Nerelimomab; Oral mucositis therapy, Avaxia; Ozoralizumab; Revamilast; TgAAC94; Thalidomide, Celge

Table 1					All drugs		
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications	
TNF continued	tumor necrosis factor	Neonatal lupus	10	rs3099844-? (0.11)	Neonatal lupus	Respiratory distress syndrome, adult; Retinopathy, general; Sarcoidosis; Sepsis; Spondyloarthritis, axial; Transplant rejection, bone marrow; Transplant rejection, general; Ulcer, aphthous; Uveitis; Vaccine adjunct; Wegener's granulomatosis; Xerophthalmia	
TNFRSF1A	tumor necrosis factor receptor superfamily, member 1A	Primary biliary cirrhosis	26	rs1800693-C (0.40)	Primary biliary cirrhosis	AKH-217; AP-301; ARRY-438162; CC-11050; CR-1; ITMN-520; PMI-005; TNF-K; TNF-alpha, CytImmune; TNFR1 NAM, Addex; TT-301; VB-111; YP-008; Anti-TNFMab, LG Life Sciences; Apremilast; Citoplurikin; Lenercept; Pirfenidone; Pirfenidone, GNI; Semapimod sa	

Table 1		Strongest SNP-Risk Allele (frequency)			New suggested indication	Current indications	All drugs
Gene	Description	GWAS phenotype	No. of associated genes				
TNFRSF21	tumor necrosis factor receptor superfamily, member 21	Panic disorder	10	rs2103868-? (0.26)	Panic disorder	Multiple sclerosis, general	DR6 antagonist, Biogen Id
TNFRSF9	tumor necrosis factor receptor superfamily, member 9	Celiac disease	65	rs12727642-A (0.19)	Celiac disease	Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, solid, general	PF-050825
TNFRSF9	tumor necrosis factor receptor superfamily, member 9	Ulcerative colitis	96	rs35675666-G (0.83)	Ulcerative colitis	Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, solid, general	PF-050825
TNFSF11	tumor necrosis factor (ligand) superfamily, member 11	Crohn's disease	83	rs2062305-G (0.35)	Crohn's disease	Arthritis, rheumatoid; Bone disorder, general; Cancer, bone; Cancer, breast; Cancer, colorectal; Cancer, head and neck; Cancer, lung, non-small cell; Cancer, lymphoma, Hodgkin's; Cancer, lymphoma, general; Cancer, lymphoma, non-Hodgkin's; Cancer, myeloma; Cancer, prostate; Cancer, renal; Cancer, thyroid; Hypercalcaemia of malignancy; Osteoporosis; Regeneration, bone; Regeneration, bone, fracture healing	ALX-0141; CEP-37251; GST-RANKL, Auxeris; Denosumab; Denosumab, BioXpre
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Crohn's disease	83	rs3810936-C (0.68), rs4263839-G (0.68)	Crohn's disease	Asthma	Inhibic
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Ulcerative colitis	96	rs4246905-C (0.71)	Ulcerative colitis	Asthma	Inhibic
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Inflammatory bowel disease	17	rs6478109-? (0.69)	Inflammatory bowel disease	Asthma	Inhibic
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Leprosy	4	rs6478108-A (0.46)	Leprosy	Asthma	Inhibic

Table 1		Strongest			New suggested indication	Current indications	All drugs
		Description	GWAS phenotype	No. of associated genes			
Gene							
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	Celiac disease	65	rs859637-A (0.49)	Celiac disease	Asthma; Rhinitis, allergic, general	Oxelumab (I)
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	Diabetic retinopathy	34	rs1342038-G (0.64)	Diabetic retinopathy	Asthma; Rhinitis, allergic, general	Oxelumab (I)
TNFSF4	tumor necrosis factor (ligand) superfamily, member 4	Systemic lupus erythematosus	42	rs2205960-A (0.27)	Systemic lupus erythematosus	Asthma; Rhinitis, allergic, general	Oxelumab (I)
TRHR	thyrotropin-releasing hormone receptor	Body mass	1	rs7832552-T (0.32)	Body mass	Alzheimer's disease; Amnesia; Ataxia, spinocerebellar; Dementia, vascular; Depression, general; Diagnosis, general; Dyskinesia, general; Epilepsy, general; Head trauma; Ischaemia, cerebral	54580; JTP-2942; TRH, Daiichi; TRH, Ferring; TRH, Japan Tobacco; Montirelin hydrate; Posatirelin; Protirelin, Takeda; Taltirelin hydrate; Taltirelin hydrate O
TRPM8	transient receptor potential cation channel, subfamily M, member 8	Migraine	7	rs10166942-T (0.81)	Migraine	Cancer, breast; Cancer, colorectal; Cancer, lung, general; Cancer, prostate; Cancer, solid, general; Pain, general	D-3263; TRPM8 antagonists, Johnson & Johnson; TRPM8, Hydra Bioscienc
TSHR	thyroid stimulating hormone receptor	Optic disc size	17	rs17111394-T (NR)	Optic disc size	Cancer, thyroid; Diagnosis, cancer; Goitre, non-toxic	Thyrotropin alfa, Sano
TYK2	tyrosine kinase 2	Type 1 diabetes	50	rs2304256-C (0.71)	Type 1 diabetes	Arthritis, rheumatoid; Cancer, haematological, general; Cancer, solid, general	SGL-1252; Rheumatoid arthritis therapy, SRI Internation
TYK2	tyrosine kinase 2	Crohn's disease	83	rs12720356-G (0.08)	Crohn's disease	Arthritis, rheumatoid; Cancer, haematological, general; Cancer, solid, general	SGL-1252; Rheumatoid arthritis therapy, SRI Internation
TYK2	tyrosine kinase 2	Psoriasis	30	rs12720356-A (0.90), rs280519-A (0.47)	Psoriasis	Arthritis, rheumatoid; Cancer, haematological, general; Cancer, solid, general	SGL-1252; Rheumatoid arthritis therapy, SRI Internation
TYR	tyrosinase (oculocutaneous albinism IA)	Melanoma	4	rs1393350-A (0.27)	Melanoma	Cancer, melanoma; Skin disorder, general	MKC-1106-MT; Kojic acid, Vinas; Melanoma vaccine, Bavarian; Melanoma vaccine, Ich

Table 1		Strongest SNP-Risk Allele (frequency)			Current indications			All drugs	
Gene	Description	GWAS phenotype	No. of associated genes	New suggested indication					
TYR	tyrosinase (oculocutaneous albinism IA)	Vitiligo	25	Vitiligo	Cancer, melanoma; Skin disorder, general			MKC-1106-MT; Kojic acid, Vinas; Melanoma vaccine, Bavarian; Melanoma vaccine, Ich	
VEGFA	vascular endothelial growth factor A	Chronic kidney disease	67	Chronic kidney disease	Amyotrophic lateral sclerosis; Arthritis, rheumatoid; Atherosclerosis; Cancer, basal cell; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, stomach; Cancer, gastrointestinal, stromal; Cancer, general; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, mast cell; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, pancreatic; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, Kaposi's; Cancer, sarcoma, general; Cancer, sarcoma, soft tissue; Cancer, solid, general; Cancer, thyroid; Cardiomyopathy, ischaemic; Dysplasia, general; Glaucoma; Head trauma; Herpetic keratitis; Macular degeneration, age-related, general; Macular degeneration, age-related, wet; Malignant ascites; Mastocytosis; Myelodysplastic syndrome; Myopia; Nephropathy, diabetic; Neurofibromatosis; Neuropathy, diabetic; Neuropathy, unspecified; Oedema, macular; Oedema, macular, diabetic; Peripheral vascular disease; Psoriasis; Retinal vein occlusion; Retinopathy, diabetic; Spinal cord injury			AG-13958; ALN-VSP; ALS gene therapy, Oxford BioM; BFH-772; CEQ-300; CVX-241; IXSVEGF; KH-902; MP-0112; MultiGeneAngio; NT-502; NT-503; PAN-90806; PRS-050; PTC-299; SB-509; STP-601; STP-801; VEGF gene therapy, Human Stem Cells Institute; VEGF gene therapy, Merck; VEGF inhibitors, Santen; VEGF peptide, Johnson & Johnson; VEGF-2 gene therapy, VIA; X-82; Aflibercept; Aflibercept ophthalmic solution; Bevacizumab; Bevacizumab, BioXpress; Bevasiranib sodium; Lycium anti-angiogenic proteoglycan, Retina Pharma; Midostaurin; Pegaptanib octasodium; Pegaptanib sodium, extended release, Eyetech; Ranibizumab; SFLT-01 gene therapy, AG	

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
VEGFA	vascular endothelial growth factor A	Type 2 diabetes	61	rs9472138-T (0.28)	Type 2 diabetes	Amyotrophic lateral sclerosis; Arthritis, rheumatoid; Atherosclerosis; Cancer, basal cell; Cancer, bladder; Cancer, brain; Cancer, breast; Cancer, colorectal; Cancer, endometrial; Cancer, fallopian tube; Cancer, gastrointestinal, stomach; Cancer, gastrointestinal, stromal; Cancer, general; Cancer, head and neck; Cancer, leukaemia, acute myelogenous; Cancer, leukaemia, chronic lymphocytic; Cancer, leukaemia, mast cell; Cancer, liver; Cancer, lung, non-small cell; Cancer, lung, small cell; Cancer, lymphoma, B-cell; Cancer, lymphoma, non-Hodgkin's; Cancer, melanoma; Cancer, mesothelioma; Cancer, myeloma; Cancer, neuroendocrine, carcinoid; Cancer, neuroendocrine, pancreatic; Cancer, ovarian; Cancer, pancreatic; Cancer, peritoneal; Cancer, prostate; Cancer, renal; Cancer, sarcoma, Kaposi's; Cancer, sarcoma, general; Cancer, sarcoma, soft tissue; Cancer, solid, general; Cancer, thyroid; Cardiomyopathy, ischaemic; Dysplasia, general; Glaucoma; Head trauma; Herpetic keratitis; Macular degeneration, age-related, general; Macular degeneration, age-related, wet; Malignant ascites; Mastocytosis; Myelodysplastic syndrome; Myopia; Nephropathy, diabetic; Neurofibromatosis; Neuropathy, diabetic; Neuropathy, unspecified; Oedema, macular; Oedema, macular, diabetic; Peripheral vascular disease; Psoriasis; Retinal vein occlusion; Retinopathy, diabetic; Spinal cord injury
VKORC1	vitamin K epoxide reductase complex, subunit 1	Warfarin maintenance dose	4	rs10871454-? (NR), rs9923231-? (NR), rs9923231-T (0.40)	Warfarin maintenance dose	Ischaemia, cerebral; Thrombosis, general; Thrombosis, venous
						AG-13958; ALN-VSP; ALS gene therapy, Oxford BioM; BFH-772; CEQ-300; CVX-241; IXSVEGF; KH-902; MP-0112; MultiGeneAngio; NT-502; NT-503; PAN-90806; PRS-050; PTC-299; SB-509; STP-601; STP-801; VEGF gene therapy, Human Stem Cells Institute; VEGF gene therapy, Merck; VEGF inhibitors, Santen; VEGF peptide, Johnson & Johnson; VEGF-2 gene therapy, VIA; X-82; Aflibercept; Aflibercept ophthalmic solution; Bevacizumab; Bevacizumab, BioXpress; Bevasiranib sodium; Lycium anti-angiogenic proteoglycan, Retina Pharma; Midostaurin; Pegaptanib octasodium; Pegaptanib sodium, extended release, Eyetech; Ranibizumab; SFLT-01 gene therapy, AG
						Tecarfar

Table 1						
Gene	Description	GWAS phenotype	No. of associated genes	Strongest SNP-Risk Allele (frequency)	New suggested indication	Current indications
YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	Multiple sclerosis	59	rs17149161-A (0.2), rs7779014-T (0.2)	Multiple sclerosis	Fibrosis, pulmonary, idiopathic; Wound healing
						All drugs
						AZX-1

The invention is further described by the following non-limiting examples.

EXAMPLES

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Example 1: Drug repositioning as a proposed short-term clinical benefit from genome-wide association studies.

It is widely recognized that Genome Wide Association Studies (GWAS) have not met their broad promise to improve human health, yet an original specific GWAS aim was to identify new drug targets. In an attempt to evaluate the utility of GWAS for new drug targets, we investigated whether GWAS studies could point to unsuspected indications for existing drugs or drugs in development. Our analyses were based on all available data in the NHGRI GWAS catalogue as of February, 2011, comprising 4818 genetic associations in 796 publications, of which 1,515 are replicated associations (p value > 1E-7) with non-anthropomorphic traits. 991 genes with HUGO names were identified from these replicated associations. A total of 212 (21%) and 469 (47%) of these genes encode proteins respectively considered as “druggable” by small molecules or biopharmaceuticals; i.e., GWAS-derived genes are significantly more likely than chance to be theoretically tractable drug targets. Of these, 155 genes (16%) are active targets for drug discovery or development programs in the pharmaceutical industry, a proportion which is 2.5 times the genome at large (6%); i.e., GWAS-identified genes are also practically more likely than chance to be drug targets. Many of the indications in these active drug targets match or are closely related to the GWAS disease trait (63/155), an emblematic example of which is 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*), encoding the target for lipid lowering statins, and which is strongly associated with LDL-cholesterol levels by GWAS. Potential opportunities for drug repositioning are even greater, with 92/155 genes revealing a mismatch between the GWAS trait and the drug indication. Examples include the necrosis factor (ligand) superfamily, member 11 (*TNFS11*), which encodes the target of the osteoporosis drug denosumab, and was genetically associated with Crohn’s disease, and also interleukin 12A (*IL12A*), which encodes the target of the cancer drug briakinumab and is associated with primary biliary cirrhosis.

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Considered together, these analyses suggest new translational applications for GWAS-identified genes as both theoretical and practical drug targets.

Introduction

5 Over the last few years large investments have been made in genome-wide association studies (GWAS) with the expectations, among others, that these studies would lead to the identification of novel therapeutic modalities or allow selection of patients who would respond better to therapeutic interventions (The Wellcome Trust Case Control Consortium. *Nature* **447**, 661–78 (2007)). Although the results have
10 provided valuable biological insights for many common diseases (Hampe *et al.* *Nat. Genet.* **39**, 207-211 (2007) and Zeggini *et al.* *Nat. Genet.* **40**, 638-645 (2008)), the translation of the genetics findings from GWAS into the clinic remains limited and a topic of intense debate (Goldstein, D.B. *N. Engl. J. Med.* **360**, 1696-1698 (2009) and Hirschorn, J.N. *N. Engl. J. Med.* **360**, 1699-1701 (2009)). Some factors could explain
15 this situation. First, the road from a gene target to an approved marketed drug takes in general more than 10 years and most GWAS results have only been obtained over the past 4 years. Second, because the effect size of the common variants identified by GWAS, alone or in aggregation, is generally modest, the impact in terms of personalized, individually tailored medicine has been negligible at this stage.
20 Recently some general principles have been proposed for post-GWAS functional analysis of risk loci that could ultimately translate into clinical benefits (Freedman, M.L. *et al.* *Nat. Genet.* **43**, 513-518 (2011)). Here we propose a faster route based on an original and fundamental GWAS aim of identifying new drug targets: by investigating if GWAS studies can be used as a pointer to alternative or refined
25 indications for drugs in development or already on the market. We first analyzed if the genes in GWAS replicated loci are potentially amenable to pharmacological modulation. Next, we examined whether the GWAS genes are already targeted by marketed drugs or by those currently being developed by the pharmaceutical industry. We hypothesized that, when the disease indication of the drug matches the GWAS
30 disease trait associated with the target gene, GWAS studies increase the confidence that the right indication is pursued and that, conversely, a mismatch would point to alternative indication for the drug, i.e. drug repositioning (Ashburn, T.T. and Thor,

K.B. *Nat. Rev. Drug. Discov.* **3**, 673-683 (2004)). This approach is particularly attractive because choosing the right indication is a major challenge in drug discovery and development, and is even more relevant for molecules already in phase II and beyond, for which a large body of data is usually available to show their safety profile.

Results

GWAS associated genes as potential pharmaceutical targets

To construct a list of GWAS genes associated with disease traits we used the catalog of published GWAS studies from the National Human Genome Research Institute (NHGRI) (<http://www.genome.gov/gwasstudies>) (Hindorff, L.A. *et al. Proc. Natl. Acad. Sci. USA* **106**, 9362-9367 (2009)). This resource contains an exhaustive description of trait/disease-associated Single Nucleotide Polymorphisms (SNP). At the time of our analysis (Feb 14, 2011) the GWAS catalog contained 796 publications with 4,818 rows of data, each row corresponding to an association between a trait and an index SNP. The analysis workflow we used is described in Figure 1 (see Methods for details). As a first step we eliminated 2,166 associations annotated as not replicated, and an additional 737 associations with p-value > 1e-7, in an attempt to minimize the inclusion of false positive signals in our analysis. An additional 400 associations were excluded because the associated traits were anthropometric and not relevant in the drug discovery context of our analysis (see Table 1). The remaining 1,515 rows from 361 publications referred to 1,099 gene names. Of these genes, 991 were recognizable as approved HUGO gene names from Entrez Gene (Maglott, D. *et al. Nucl. Acids Res.* **39**, D52-D57 (2011)). These 991 genes constituted the starting list for further analysis.

We next investigated how many of these 991 genes were amenable to pharmacological modulation using small molecules (in other words “druggable” (Hopkins, A.L. and Groom C.R. *Nat. Rev. Drug Discov.* **1**, 727-730 (2002))), or biopharmaceuticals (in other words “biopharmable” using therapeutic antibodies or protein therapeutics), and compared these results with the entire genome. Out of 991

genes, 212 (21%) were considered “druggable” by small molecules, and 469 (47%) potentially “biopharmable”, defined here as being annotated with either a signal peptide or a transmembrane domain in ENSEMBL. These proportions are higher than those derived from the entire genome (corresponding to 19,258 genes with HUGO names (Seal, R.L. *et al. Nucl. Acids Res.* 39, D514-D519 (2011)) derived from the ENSEMBL database (Flicek, P. *et al. Nucl. Acids Res.* 39, D800-D806 (2011)), which contains 3,191 potentially “druggable” genes (17%, with $p < 5E-5$) and 7,411 potentially “biopharmable” genes (38%, with $p < 6E-9$) (Figure 1).

Next we investigated if that excess in “druggable” or “biopharmable” genes among GWAS genes explained by differences in the proportion of housekeeping genes. We obtained a set of 2,375 housekeepers (Dezső, Z. *et al. BMC Biology* 6, 49 (2008)) and observed that 105 of these genes overlapped with the GWAS set of 991 genes compared to an expected 122 ($p < 0.10$). This is only slightly less than expected 122 ($p < 0.1$). Thus, housekeeping genes are marginally underrepresented in the GWAS selected genes. It is possible that housekeepers and other structural proteins may reduce the effective genome size for both disease association and practical pharmaceutical intervention. Consistent with this hypothesis, gene transcripts from the Online Mendelian Inheritance in Man (OMIM) database (Hamberger, J. *et al. Nucl. Acids Res.* 37, D793-796 (2008)) are, like our GWAS selected genes, enriched with therapeutically tractable genes with 259 of 2402 genes associated with Mendelian diseases overlapping with the our set of 991 genes, ($p = 3.4e-33$). However it is possible results from GWAS make it into OMIM potentially introducing an ascertainment bias

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Taken together, this analysis shows that GWAS genes are significantly more likely to be theoretically “druggable” or “biopharmable” targets than expected by chance. This observation prompted us to investigate which of these GWAS genes are currently pursued as targets by drugs and for what disease indication.

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Drugs targeting GWAS associated genes

We investigated how many of the 991 GWAS associated genes are targeted by drugs already launched or in development (preclinical and clinical). Pharmaprojects (<http://www.pharmaprojects.com>), a resource compiling worldwide drug and biopharmaceutical discovery pipeline data, provides a comprehensive list of drug projects and their putative targets.

From the Pharmaprojects database, we identified 1,089 genes (corresponding to 6% of the genome) being pursued as a target by a launched small molecule or biopharmaceutical, a candidate in clinical phase (annotated as Phase I to Phase III, pre-registration or registered) or in preclinical development. Terminated entries in the Pharmaprojects database were not included in our analysis, though these could provide additional examples of repositioning in future analyses. Of the 991 selected GWAS genes, 155 (16%, $p < 3E-34$) had an associated drug project (Figure 1). This excess was compatible with drug target genes being particularly important in human biology, as even slight variations within these genes (i.e. SNPs) are associated with human diseases/traits. Compared to 1,089 of 19,258 human genes, the GWAS gene set is enriched 2.7-fold in targets pursued by drugs, which is more than expected by chance (15.6% vs 5.7%, $p < 3.5e-34$). This extends the theoretical expectation of GWAS druggability to practical application in real and candidate drug molecules. It is important to note that this analysis included small molecules, biologicals (including protein therapeutics and monoclonal antibodies) but also other modalities such as antisense drugs.

We then compared the disease indications pursued by the drugs with the GWAS trait for each of these 155 genes to identify matches and mismatches in disease/indications. The analysis was done manually because the disease related terms use different vocabularies in the catalogue of GWAS studies and Pharmaprojects (see methods and supplementary information). On closer inspection, a total of 17 additional rows were eliminated where the GWAS traits did not correspond to a disease indication (this was the case for instance for CRP levels). We identified 97 matches between a drug indication and a GWAS trait corresponding to 63 individual genes and 52 GWAS traits (Figure 1); these observations could be considered as

supportive for the particular indication being pursued. In contrast, we also detected 123 mismatches, which included 51 GWAS traits and 92 individual genes (Figure 1). These mismatch findings could be the basis for drug repositioning opportunities.

5 GWAS studies supporting a drug indication

Table 3 contains 12 selected examples of matches between a GWAS trait and a drug indication for the associated GWAS gene. One of the best known examples of an identical match is the 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) gene. The product of *HMGCR* is targeted by statins, a well known class of cholesterol lowering medications, and SNPs within this gene have been unambiguously associated with LDL cholesterol levels in multiple GWAS studies (Kathiresan, S. *et al. Nat. Genet.* **40**, 189-197 (2008) and (Burkhardt, R. *et al. Arterioscler. Thromb. Vasc. Biol.* **28**, 2078-2084 (2008)). An additional example is the interleukin 12B gene (*IL12B*). *IL12B* has been associated through GWAS with autoimmune inflammatory diseases such as Crohn's (Barrett, J.C. *et al. Nat. Genet.* **40**, 955-962 (2008) and psoriasis (Nair, R.P. *et al. Nat. Genet.* **41**, 199-204 (2009) and there is an approved human monoclonal antibody (mAb) Ustekinumab (Centocor/Janssen-Cilag), targeting *IL12B*, currently marketed for psoriasis and with a Phase II program for Crohn's disease. For less advanced drug development programs a match could provide more confidence for the disease indication. For example, Mellitech is a small Biotech company that has a preclinical program for type 2 diabetes with small molecule agonists of the solute carrier family 30 (zinc transporter) member 8 gene (*SLC30A8*). Several GWAS studies (Scott, L.G. *et al. Science* **316**, 1341-1345 (2007) and Zeggini, E. *et al. Science* **316**, 1336-1341 (2007)) have associated *SLC30A8* with type 2 diabetes providing additional reasons to believe in this target for type 2 diabetes, unless of course this program was initiated based on these GWAS studies in the first place.

Tables 2 and 3 also include examples where the GWAS trait is closely related, but not identical to the drug indication reported in Pharmaprojects for the drug of the same target gene. These imperfect matches may pinpoint the right disease indication

for the drug. An example is the alpha interleukin 2 receptor (*ILR2A*) gene that has been associated with Crohn's disease in GWAS (Franke, A. *et al. Nat. Genet.* **42**, 1118-1125 (2010) (see Table 2 and 3). A monoclonal antibody for *ILR2A* (Novartis) is currently in Phase II to treat ulcerative colitis. Both Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases but at the time of the analysis *ILR2A* was not associated with ulcerative colitis by GWAS. The GWAS association with Crohn's suggests that pursuing that indication in addition to ulcerative colitis could be attractive. Other instances of imperfect matches are for cancer indications. For example the cyclin E1 gene (*CCNE1*) has been associated with bladder cancer in GWAS (Rohtman, N. *et al. Nat. Genet.* **42**, 978-984 (2010)) and is targeted by drugs in Phases I and II identified in the Pharmaprojects database. This class of molecules have been designed to treat a variety of cancer types; however, none of them has been specifically tested for bladder cancer. GWAS information points here to this particular indication.

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GWAS suggesting drug repositioning opportunities

Table 4 highlights 12 selected examples of drug repositioning opportunities based on 123 mismatches between a GWAS disease trait and a drug indication (for complete list see Table 1 and 2 as well). For example, denosumab (*Prolia*® Amgen/GSK) is a marketed drug indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. *Denosumab* targets the gene tumor necrosis factor (ligand) superfamily, member 11 (*TNFSF11*) also known as *RANKL*. *TNFSF11* has been associated with Crohn's disease by GWAS (Franke, A. *et al.*) and may potentially play a role in inflammatory bowel disease (Ahscroft *et al. Immunity* **19**, 849-861 (2003) and Moschen *et al. Gut* **54**, 479-487 (2005)). More work is required to understand mechanistically the role of *TNFSF11*, but it is tempting to speculate that *denosumab* could be re-purposed with a Crohn's disease indication through additional clinical trials. Another drug in advanced development that is also a potential drug repositioning opportunity is RPI-78M (Nutra Pharma). RPI-78M induces interleukin 27 (*IL27*) and gamma-interferon, and it is in Phase III testing for Adrenoleukodystrophy and for additional diseases such as multiple sclerosis and

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herpes virus infection in earlier phases. *IL27* has also been associated with inflammatory bowel disease (Imielinski, M. *et al. Nat. Genet.* **41**, 1335-1340 (2009)), including Crohn's disease (Franke, A. *et al.*) in GWAS. Recently, it has been shown that treatment with IL-27 reduces experimental colitis through the suppression of several inflammatory cytokines including IL-17 (Sasaoka, T. *et al. Am. J. Physiol. Gastrointest. Liver Physiol.* **300**, G568-G576 (2011)). In this situation, human genetic and animal studies converge to support inflammatory bowel disease and Crohn's disease specifically as new indications for RPI-78M. A phase I example is for the antibody Biib-033 from Biogen Idec Inc. targeting the leucine rich repeat and Ig domain containing 1 (*LINGO-1*) gene. Biib-033 is being developed for patients with multiple sclerosis. Several pieces of evidence support *LINGO1* as an attractive target for this indication (Mi, S. *et al. Int. J. of Biochem. and Cell. Biol.* **40**, 1971-1978). Interestingly a GWAS result suggests that *LINGO1* may also be an attractive target for essential tremor, a neurological disorder (Stefansson, H. *et al. Nat. Genet* **41**, 277-279 (2009); Clark, L.N. *et al. Eur. J. of Hum. Genet.* **18**, 838-843 (2010); and Thier, S. *et al. Mov. Disord.* **25**, 709-715 (2010)). Essential tremor is most commonly treated, with limited success, by beta blockers, antiepileptics or anticonvulsants and for most severe cases a surgical procedure is sometimes used (Louis, E.D. *Lancet Neurol.* **4**, 100-110 (2005)). Therefore it would seem attractive to consider essential tremor as a new indication in the clinical development plan of Biib-033 or more broadly for *LINGO1* inhibitors. A preclinical example is Inhibicor (Heat Biologics), an antibody based biological that blocks the tumor necrosis factor (ligand) superfamily, member 15 gene (*TNFSF15*) which is being investigated in preclinical research for asthma. *TNFSF15* has been associated by GWAS with three related traits: Crohn's disease (Barrett, et al. and Franke, et al.) ulcerative colitis (Anderson, C.A. *et al. Nat. Genet.* **43**, 246-252 (2011), and overall inflammatory bowel disease (Chaudhary, D. and Kasaian, M. *Curr. Op. in Inv. Drugs* **7**, 432-437 (2006)). In addition to the GWAS data, several lines of evidence suggest that *TNFSF15* could be an attractive target for these diseases. *TNFSF15* may play an important role in a Th1-mediated disease such as Crohn's disease (Bamias, G. *et al. J. of Imm.* **171**, 4868-4874 (2003)) and has also been identified as an important modulator in the development of chronic mucosal inflammation by enhancing T(H)1 and T(H)17 effector functions

(Takedatsu, H. *et al. Gastroenterology* **135**, 552-567 (2008). More recently it was shown that up-regulation of *TNFSF15* expression can promote mucosal inflammation and gut fibrosis (Shih, D.Q, *et al. PloS One* **6**(1), e16090 (2011). The combination of this information with the GWAS findings and the fact that Inhibicor blocks *TNFSF15* suggests that repositioning that drug for Crohn's or ulcerative colitis is worthy of consideration.

The selected examples discussed above, have additional supporting information to support alternative indications for these drugs. Other mismatches in Table 4 have less additional support, but are possibly more novel, and thus could provide unexpected drug repositioning possibilities. Such a mismatch is for the dopamine beta-hydroxylase (*DBH*) gene. Nepicastat (Hoffman-La Roche) is an inhibitor of *DBH* in phase II development for cocaine addiction and post-traumatic stress disorder. *DBH* has also been associated in GWAS with smoking cessation (Tobacco and Genetics Consortium *Nat. Genet.* **42**, 441-447 (2010)). It is thus tempting to speculate that *DBH* inhibitors may be beneficial for smoking cessation, while acknowledging that the direction of effect is not known yet. Another such example is the interleukin 12A (*IL12A*) gene. Many drugs are being developed to target *IL12A* from preclinical to Phase III. Some are monoclonal antibodies such as briakinumab (Abbott), others are gene therapies such as EGEN-001 (Egen) with replacement *IL12A*. A range of indications are being pursued including psoriasis, Crohn's disease and many cancers. Several GWAS have found an association between *IL12A* and primary biliary cirrhosis Hirschfield, G.M. *et al. N. Eng. J of Med.* **360**, 2544-2555 (2009); Liu, X. *et al. Nat. Genet.* **42**, 658-660 (2010); and Mells, G.F. *et al. Nat. Genet.* **42**, 329-332 (2010)). In this example the genetics from the GWAS appears to be the only validation of the target for biliary cirrhosis and it is possible that these *IL12A* drugs could be used to treat primary biliary cirrhosis. These cases of indication mismatch in Table 4, with little additional evidence other than the GWAS, will require more investigation, including experimental work. At the same time they could provide genuinely novel opportunities for drug repositioning.

Not all mismatches will lead to successful drug repositioning opportunities. An illustration comes from the nitric oxide synthase 2, inducible gene (*NOS2*). A range of inhibitors are under development for various disease indications such as mucositis, rheumatoid arthritis, pain and cerebral ischaemia. Recently, SNPs within
5 *NOS2* have been associated in GWAS with psoriasis (Stuart, P.E. *et al. Nat Genet.* **42**, 1000-1004 (2010)), raising the possibility that psoriasis may be an attractive new indication for this class of drugs. This possibility was supported by the observations that skin lesions of psoriatic patients show an increase in nitric oxide production (Ormerod, A.D. *et al. Arch. Dermatol. Res.* **290**, 3-8 (1998)). Contrary to these
10 expectations, at least one small study did not identify any clinical improvement when a topical inhibitor of nitric oxide synthesis was applied in 17 psoriatic subjects (Ormerod, A.D. *et al. Br. J. Dermatol.* **142**, 985-990 (2000)). Another example is for the *HMGCR* gene, which has been associated with body mass index (BMI) by GWAS (Speliotes, E.K. *et al. Nat. Genet.* **42**, 937-948 (2010)). However no impact on BMI
15 has been reported in large numbers of patients treated with statins (Heart Protection Study Collaborative Group *Lancet* **360**, 7-22 (2002)). Negative studies are rarely definitive, but these two examples highlight some of the limitations of the approach proposed here.

20 Examples of predicted new indications for certain drug classes are presented in Table 2.

Table 2
GWAS Trait could be a new indication

Target	Full name of target	Pharmaceutical	Current indication	New predicted Indication	Drug class for new indication
DBH	dopamine beta-hydroxylase (dopamine beta-monooxygenase)	Nepicastat	Peripheral vascular disease; Post-traumatic stress disorder; Cocaine dependence.	smoking cessation	Inhibitor
IL2RA	interleukin 2 receptor, alpha	Aldesleukin; mAbs	Cancer	Type 1 Diabetes	IL2/mAb
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	Inhibitor	Asthma	Crohn/IBD	Inhibitor
TNFSF11	tumor necrosis factor (ligand) superfamily, member 11	Denosumab	Osteoporosis/bone cancer/Cancer	Crohn's disease	mAb/Antagonists
MTNR1	melatonin receptor 1B	Melatonin	Depression/Clock/Migraine	T2DM	some evidence that antagonists have been explored
IL13	interleukin 13	GSK anti-IL13	Asthma (failed)	Psoriasis	Inhibitors
IL-10	interleukin 10	avi-2; Eg-10; Hmpl-011; Interleukin-10	RA/Crohn/	Behcet	Inhibitors/Activators
LINGO1	leucine rich repeat and Ig domain containing 1	Biib-033	MS	Essential tremor	Inhibitor (+mAb in PC)
CSF1	colony stimulating factor 1 (macrophage)	Tg-3003	Cancer	Paget	Pathway blocker
HDAC		Valproate	Epilepsy	AD	
		Vorinostat	Adjuvant BC	AD	
CR1	complement component (3b/4b) receptor 1	Candida hp; Cdx-1135; Eti-204; Eti-211	Infection, Candida; renal failure	AD	both directions
CLU	clusterin	Ab-16b5; Clustirsen	Cancer	AD	Inhibitors
ICOSLG	inducible T-cell co-stimulator ligand	Amg-557	SLE	Crohn/Celiac	

Table 2

GWAS Trait could be a new indication

Target	Full name of target	Pharmaceutical	Current indication	New predicted Indication	Drug class for new indication
IL18R	Interleukin 18 receptor	IL18R antag	Psoriasis	Crohn/IBD	Inhibitor
IL27	Interleukin 27	Rpi-78m	Adrenoleukodystrophy; Infection, herpes virus, general; Infection, varicella zoster virus; Multiple sclerosis, general; Myasthenia gravis	Crohn/IBD	Inducer of IL27 expression
IL12A	Interleukin 12A	Briakinumab; Cancer gene therapy, intrexon; Egen-001; Gx-110; Interleukin-12, neumedicines	Cancer/Crohn/Psoriasis/Infection	Primary biliary cirrhosis	Both
TERT	telomerase reverse transcriptase	Vaccines (PhIII)/TAT153 (PC)	Cancer; fibrosis hepatic, pulmonary; Anaemia aplastic	IPF	Inhibitors; Activators
IL-2/IL-2R	Interleukin 2/Interleukin2 receptor	Anti-IL-2 MaB	inflammatory diseases	Crohn/IBD/vitiligo	
IL2RA	interleukin 2 receptor, alpha	IL2RA mAb	UC	Crohn's disease	
IL23R	Interleukin 22 receptor	Apg-2305; Fm-202	Arthritis, psoriatic; Psoriasis	Crohn/IBD/Behcet	Inhibitor (ATX3105); allosteric modulator

GWAS pointing to wrong indication

HMGCoAR		Statins	LDL lowering	BMI	
NOS2	nitric oxide synthase 2, inducible	NOS2 inhibitors	Inflammatory	Psoriasis	

GWAS pointing to safety signal (i.e. opposite direction)

MUC1	mucin 1, cell surface associated	Anti-mucin Mab	cancer	Crohn	mAb
TCF4	transcription factor 4	Cwp-231	cancer	Fuchs's corneal dystrophy	

Selected examples of GWAS studies supporting drug indications: in each example the GWAS trait is identical (rows 1, 2, 3, 8,10 and 11) or closely related (rows 4, 5, 6, 7, 9 and 12) to the drug indication. Examples are ranked from most advanced drug (launched) to less advanced (Preclinical). The associated gene between each GWAS and the drug is shown. The drug indication and the phase of development for each drug are derived from the Pharmaprojects database. In many cases more drugs for the gene are listed in the database at different phases. The GWAS references are from the catalog of GWAS studies (<http://www.genome.gov/gwasstudies>). See Table 3.

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Table 3

Drug Name	Most Advanced Development Phase (for the indication)	Gene	Drug Indication	GWAS Trait	GWAS Reference
Statins	Launched	<i>HMGCR</i>	Hypercholesterolaemia	LDL Cholesterol	16,17
Ustekinumab	Approved	<i>IL12B</i>	Psoriasis	Psoriasis	19
Azimilide	III	<i>KCNQ1</i>	Ventricular fibrillation	QT interval	50,51
Ustekinumab	II	<i>IL12B</i>	Crohn' s disease	Crohn's disease	18
anti-IL2 receptor mAb	II	<i>IL2RA</i>	Ulcerative colitis	Crohn's disease	22
TTP-399	II	<i>GCK</i>	Type 2 diabetes	Fasting glucose-related traits	52,53
AMG-785/CDP-7851	II	<i>SOST</i>	Bone regeneration/ Osteoporosis	Bone mineral density	54
PRX-302	II	<i>KLK3</i>	Prostate cancer	Serum prostate-specific antigen levels/ Prostate cancer	55,56
CYC-202	I/II	<i>CCNE1</i>	Various cancers (not Bladder)	Bladder cancer	23
ASP2408	I	<i>CTLA4</i>	Rheumatoid arthritis	Rheumatoid arthritis	57,58
Znt8 agonists	Preclinical	<i>SLC30A8</i>	Type 2 diabetes	Type 2 diabetes	20,21
TAT-153	Preclinical	<i>TERT</i>	Pulmonary fibrosis	Idiopathic pulmonary fibrosis	59

Selected examples of potential opportunities to reposition a drug for a new disease indication based on the GWAS trait. Examples are ranked from most advanced drug (launched) to less advanced (Preclinical). The associated gene between each GWAS and the drug is shown. The drug indication and the phase of development for each drug are derived from the Pharmaprojects database. In many cases more drugs for the gene are listed in the database at different phases. The GWAS references are from the catalog of GWAS studies

(<http://www.genome.gov/gwasstudies>). For the full list, see table 4 in the supplementary material. See table 4.

Table 4

Drug Name	Most Advanced Development Phase (for the indication)	Gene	Drug Indication	GWAS Trait	GWAS Reference
Denosumab/AMG-162	Launched/registered	<i>TNFSF11</i>	Osteoporosis/Bone cancer	Crohn's disease	22
RPI-78M	III	<i>IL27</i>	Adrenoleukodystrophy	Crohn's disease/Inflammatory bowel disease	22,26
Azimilide	III	<i>KCNQ1</i>	Ventricular fibrillation	Type 2 diabetes	60,61,62
Briakinumab/EGEN-001	III/II	<i>IL12A</i>	Psoriasis/Cancer	Primary biliary cirrhosis	40,41,42
ACN-189/AEB-071	II	<i>PRKCQ</i>	Psoriasis/Uveitis	Type 1 diabetes	63,64
Oxelumab	II	<i>TNFSF4</i>	Asthma	Systemic lupus erythematosus	65
Nepicastat	II	<i>DBH</i>	Cocaine addiction/post-traumatic stress disorder	Smoking cessation	44
NOX-A12	I	<i>CXCL12</i>	Cancer/Stem cell mobilization	Coronary heart disease	66,67
Biib-033	I	<i>LINGO-1</i>	Multiple sclerosis	Essential Tremor	35
AMG-557	I	<i>ICOSLG</i>	Systemic lupus erythematosus	Crohn's disease/Celiac disease/Ulcerative colitis	21,40,52
Inhibicor	Preclinical	<i>TNFSF15</i>	Asthma	Crohn's disease/Inflammatory bowel disease/Ulcerative colitis	21,25,39,40
Cwp-231	Preclinical	<i>TCF4</i>	Cancer	Fuchs's corneal dystrophy	68

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Discussion

In the present analysis, we provide evidence that GWAS studies do not only provide insights into the biology of diseases, but may provide an immediate translational opportunity by pointing to alternative indications for drugs. First, we observed that the set of 991 GWAS associated genes in our analysis are significantly more likely to be amenable to modulation by small molecules or biopharmaceuticals than a random set of genes. That is, GWAS-identified genes offer theoretically greater chances of being “druggable” or “biopharmable” than otherwise random genes. Next, we found that 155 of those genes which are the targets of drugs active in

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pharmaceutical pipelines, a number which is significantly higher than expected by chance. That is, GWAS identified genes are also practically more likely to be active drug targets. 16% of the GWAS genes are active drug targets, while only 6% of the overall genome is actively targeted by drug projects in Pharmaprojects. We classified these 155 examples of genes targeted by pipeline and marketed drugs into two groups. The first group contains instances of matches between the GWAS trait and the drug indication; these observations provide validation for the approach proposed here. It also includes close matches, i.e. instances where the GWAS trait is closely related, but not identical, to the drug indication; these observations may be used for optimal positioning of the drug. The second group contains instances of mismatches between the GWAS trait, pointing to alternative indications for existing drugs or drugs in development.

It must be noted that some GWAS positive signals are in gene-rich loci where it could be difficult to identify the driving gene. In these cases additional drug repositioning opportunities would require close scrutiny of each region individually. As an example, the 3p31 GWAS locus shows several Chemokine (C-C motif) receptor genes (*CCR1*, *CCR2*, *CCRL2*, *CCR3*, *CCR5*, *CCR9*) associated with celiac disease (Dubois, P.C. *et al. Nat. Genet.* **42**, 295-302 (2010) and Hunt, K.A. *et al. Nat. Genet.* **40**, 395-402, (2008)). A phase III drug targeting CCR9 has been developed for celiac disease whilst several drugs are targeting CCR1, CCR2, CCR3 and CCR3 but do not have celiac disease as an indication. In these instances, additional work is required to determine which of these genes is causative and, subsequently, which drug has the potential to modify the underlying condition. Our analyses are also fundamentally based on situations where the drug target matches a GWAS-identified locus. However, GWAS may hit the ligand, while drug discovery programs target the receptor, or vice versa, or the direction of effect may differ between the GWAS gene and desired drug action. These and other examples suggest that additional pathway information may be useful to further leverage the interaction of GWAS and ongoing drug development programs.

Methods

Selection of GWAS genes. GWAS data was downloaded from the NHGRI website (<http://www.genome.gov/26525384>) on February 14, 2011. There were 4,818 rows of GWAS data in this version. This table included 796 publications. We only considered replicated GWAS's, removing from consideration 2,166 rows where the Replication sample size (column 10) was blank or "NR". We also excluded 737 GWASs with p-value greater than $1e-7$, and rejected an additional 400 rows because the traits as specified in column titled *Disease/Trait* were considered anthropometric and not relevant for a disease focused analysis. The remaining 1,515 (4818-2166-737-400) rows from 361 publications referred to 1,099 gene names in column titled *Reported Gene(s)*. Of these 991 were recognizable as approved HUGO gene names from Entrez Gene. This set of 991 GWAS genes (GWAS-991) was used for further analysis.

Small molecule druggability and biopharmability of GWAS genes. We combined two sets of proteins that had been annotated as being small molecule druggable (Hopkins, A.L. and Groom C.R. *Nat. Rev. Drug Discov.* **1**, 727-730 (2002) and Russ, A.P. and Lampel, S. *Drug. Disc. Today* **10**, 1607-1610 (2005)) to generate a list of 3,191 genes (16.6% of the genome) that may possibly be considered small molecule druggable. We used a two sided Fischer exact test to determine all p-values to assess which overlaps are significant. Biopharmable proteins were defined as those accessible using an antibody or replaceable by a protein therapy. This is hard to determine precisely, but as a first approximation we defined it as those annotated with either a signal peptide or transmembrane domain in Ensembl. All protein coding human genes with HGNC symbols were exported from Biomart (www.biomart.org) along with transmembrane domain and signal domain annotation. 7,411 (38.5%) of the 19,258 Ensembl genes with HUGO names were annotated with either a signal peptide or transmembrane domain. We obtained a set of 2,375 housekeepers from Dezső *et al.* (Dezső, Z. *et al. BMC Biology* **6**, 49 (2008)). The OMIM data was downloaded on Jan 18, 2011 from <ftp://ftp.ncbi.nih.gov/repository/OMIM/morbidmap>. The Entrez gene identifiers were mapped to HUGO names for analysis using Entrez gene.

Industry pipelines analysis. Industry pipeline data for a list of all biotech and pharmaceutical projects was taken from PharmaProjects (from Informa Healthcare) as of November 1, 2010. We considered all active projects spanning preclinical to marketed drugs that listed one or more human genes as a known target and had an explicit disease indication. This comprised ~14,000 projects of which 11,462 listed 1,089 human genes as a potential target. At that stage we also disregarded 17 associations with continuous traits which did not directly represent diseases like waist-hip ratio, C-reactive protein, vertical cup-disc ratio fibrinogen levels, aortic root size or platelet aggregation. Both GWAS and Pharmaprojects use non-standard phenotype and disease indication vocabularies, so we had to manually compare them and make a subjective call as to when a GWAS phenotype was a fairly obvious or related match for a Pharmaprojects disease indication and when it was a mismatch. In this phase we considered all cancer phenotypes to match all cancer indications. This step of determining whether GWAS phenotype matches a disease indication is admittedly subjective and laborious. We did not exclude vaccines provided they listed a human target. The original publications were checked for the selected examples included in Table 3 and in the text to determine if the condition was associated unambiguously with the drug target gene or whether several genes underneath the association locus were in the vicinity, making the association ambiguous.

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Note that, like the NHGRI GWAS database, Pharmaprojects is also often updated, so additional inclusions and terminations will have occurred since the time of our database freeze.

25 CONCLUSION

One of the long-standing arguments in favor of the GWAS approach and the common disease/common variant hypothesis that underpins it, has been the potential to identify new targets or pathways for therapeutic intervention. However despite the identification of many GWAS associated genes and some new knowledge for some diseases the direct and rapid application of GWAS studies to the benefit of patients remains elusive. We investigated potential opportunities in a drug discovery context. We found that GWAS associated genes were more likely to be druggable than a

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random set of genes. We also identified a list of drugs that target GWAS genes. In some cases it provided additional support that the drug was used for the right or a related disease indication. In a few cases it also provided some exciting opportunities for drug repositioning or repurposing which is an effective way quickly to discover
 5 new efficacious and safe drugs.

Our analyses demonstrate that GWAS have the potential for both direct and indirect identification of disease-validated therapeutic targets. Although the obvious and much heralded use of genetic data for prediction and diagnosis in a personalized medicine context have not materialized, there are immediate applications in the
 10 selection of targets which are proven to be druggable, in alignment of treatment indications with appropriate therapies, in identification of new, externally validated, indicates for existing diseases, and in better understanding the pathophysiology of complex human diseases. These data offer direct validation and support for the translational utility of GWAS and also offer real therapeutic opportunities in a very
 15 short timescale.

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Example 2: Additional Indications for Drug repositioning

Based on the methods provided herein new therapeutic indications are

25 provided for drugs and biotherapeutics according to Table 1 previously shown. The column designated "New suggested indication" of the Table 1 provides new therapeutic indication determined by the methods of the present invention for the corresponding drugs and classes of therapy listed in the column designated "All drugs" of Table 1. The compounds and/or drugs presented in Table 1 can be used for

30 the treatment of at least one corresponding "New Suggested Indication" in the same row according to Table 1 and/or for the making of a medicament for the treatment of the corresponding "New Suggested Indication."

Claims:

1. A method of treating Crohn's disease in a human in need thereof, comprising administering denosumab to said human.
- 5 2. A method of treating Crohn's disease in a human in need thereof, comprising administering to said human at least one compound selected from the group consisting of: an inhibitor and/or antagonist of tumor necrosis factor ligand, a T-cell co-stimulatory ligand, an IL-18 receptor antagonist and/or inhibitor, inducer of IL27 expression, anti-IL2 receptor mAb, chemokine (C-C motif) ligand 2 inhibitor and/or antagonist, estrogen related receptor alpha binding agent, galactosylceramidase, anti-Intercellular adhesion molecule 3 (ICAM3) mAb, anti-ICOS mAb, IL-23 receptor inhibitor and/or antagonist, Janus kinase 2 inhibitor, leucine-rich repeat kinase 2 inhibitor, mucin 1, cell surface associated inhibitor, signal transducer and activator of transcription 3 (acute-phase response factor) inhibitor, and tyrosine kinase 2 inhibitor.
- 10 3. The method of claim 2 wherein the human also has Celiac disease, irritable bowel syndrome, and/or inflammatory bowel disease.
4. The method of claim 2, wherein the compound is a tumor necrosis factor ligand antagonist.
- 20 5. The method of claim 4, wherein the tumor necrosis factor ligand is member 11 or receptor activator of nuclear factor kappa-B ligand (RANKL).
6. The method of claim 4, wherein the tumor necrosis factor ligand is member 15.
7. The method of any one of claims 4 to 6, wherein said antagonist is a monoclonal antibody.
- 25 8. The method of claim 7 wherein the monoclonal antibody is humanized.
9. The method of claim 7, wherein the monoclonal antibody is a human antibody.
10. The method of claim 7, wherein said monoclonal antibody is denosumab or a functional fragment thereof.
- 30 11. The method of claim 2, wherein the compound is a T-cell co-stimulatory ligand.

12. The method of claim 11 wherein said T-cell co-stimulator is an antibody that binds B7 related proteins.
13. The method of claim 12 wherein said T-cell co-stimulator is a human antibody that binds to B7 related protein-1 (B7RP-1).
- 5 14. The method of claim 2, wherein the compound is signal transducer and activator of transcription 3 (STAT3) inhibitor.
15. The method of claim 14 wherein said compound is selected from: OPB-31121; OPB-51602; Bardoxolone methyl; Brivudine, and RESprote.
- 10 16. A method of treating multiple sclerosis in a human in need thereof, comprising administering a STAT3 inhibitor to said human.
17. A method for repositioning a pharmaceutical, comprising the steps of:
- a. selecting at least one target gene, gene product, or loci associated with the treatment of at least one first disease, trait and/or phenotype by said pharmaceutical,
 - 15 b. identifying at least one second disease, trait and/or phenotype associated with least one target gene, gene product, or loci of (a) using genome-wide associated studies, and
 - c. selecting at least one second disease, trait and/or phenotype based on step (b) for treatment with said pharmaceutical.
- 20 18. The method of claim 17, further comprising determining expression, overexpression, and/or amplification of said first target gene, gene product, or loci in said second disease, trait and/or phenotype.
19. The method of claims 17 or 18, further comprising identifying additional data and/or experimental support for target gene, gene product, or loci in said
- 25 second disease, trait and/or phenotype.
20. The method of any one of claims 17 to 19, further comprising identifying at least one SNPs in said target gene in said second disease, trait and/or phenotype.

Figures**Figure: 1**