I. Introduction
A. Clinical optometry as currently practiced is undergoing a fundamental, revolutionary transformation. This transformation will change the way optometrists understand, classify, diagnose, treat and manage disease.
B. The Human Genome Project and other revolutionary advances have started to increase and broaden the importance of genetics/genomics in all health care. This revolution will alter eye care forever, and it involves a tremendous change from the “old genetics” to the “new genetics.” Genetics is no longer an esoteric academic specialty that involves rare diseases.

II. Basic concepts
A. A new vocabulary comes with the revolution.
1. The genome is the set of all genetic information (e.g., nuclear genes/chromosomes, mitochondrial genes) in an organism. In other words, it consists of all the DNA in each human cell.
   a. DNA is made up of a variable sequence of 4 nucleotide bases (A, T, C, & G) – the “letters”
   b. A sequence of 3 bases (the “word”) codes for an amino acid.
   c. A gene (the “sentence”) codes for a protein.
   d. Chromosomes (the chapters of the “book of life”) contain the genes.
   e. The genome is the “book of life.”
2. The transcriptome is the set of all messenger RNA (mRNA) molecules or transcripts in a cell or organism.
3. The proteome is the complete set of proteins expressed by a genome, cell, tissue or organism. It is the set of expressed proteins at any given time point.
4. The metabolome is the set of all metabolites (e.g., metabolic intermediates, hormones) in an organism.
5. Systems biology is the study of an organism, viewed as an integrated and interacting network of genes, proteins and biochemical reactions which give rise to life. Instead of analyzing individual components or aspects of the organism, such as sugar metabolism or a cell nucleus, systems biologists focus on all the components and the interactions among them, all as part of one system. One of today’s challenges is to map the actions and interactions of all of the molecules in our bodies. To learn how these complex systems work, models of cells, tissues, and organs can be built. Knowing how these systems work is important for understanding how the systems fail (i.e., when disease occurs).

B. The flow of genetic information is from DNA to RNA to protein. A set of three nucleotide bases in the DNA sequence specify an amino acid in the protein sequence. Thus the “blueprint for life” consists of a 4-letter alphabet and 3-letter words.

III. Human Genome Project (HGP)
A. This was a 15-year worldwide research effort (1990-2005).
B. It was considered so important that the National Human Genome Research Institute was formed at NIH.
C. The HGP involved the sequencing of human DNA (3 billion base pairs).
D. The HGP was completed ahead of schedule and under-budget in April of 2003.
E. It identified the 20,000 to 25,000 genes in human DNA.

IV. Paradigm shift
A. The “old genetics”.
   1. The old genetics dealt with conditions caused by a mutation in a single gene or by an extra or missing chromosome or part of a chromosome.
   2. These conditions are relatively rare. Most patients are not directly affected by them. Thus, these conditions play a relatively small role in health care.
   3. The conditions are rare enough that genetics care could be provided by medical geneticists and genetic counselors, with occasional involvement of primary care providers.
B. The “new genetics”.
   1. The new genetics emerged due to knowledge derived from the HGP.
2. Essentially all medical conditions have a genetic component and can be viewed through a "genetic lens."
3. The new genetics deals with multifactorial conditions that are partly caused by mutation(s) in gene(s).
   a. Multifactorial systemic conditions include diabetes, atherosclerosis, hypertension, Alzheimer disease, colon cancer, breast cancer, etc.
   b. Multifactorial ocular conditions include the glaucomas, AMD, cataracts, myopia, diabetic retinopathy, etc.
   c. While many genes are involved, most genes have small effects.
4. These conditions are common enough that genetics care will be supplied mainly by primary care providers from many health disciplines with involvement of genetic counselors.
5. The new genetics will provide a better understanding of the non-genetic (environmental) factors in health & disease.
6. Essentially all disease is a result of genes interacting with the environment.
7. The rate of discovery of genes has accelerated due to:
   a. The International HapMap Project
   b. A profound decrease in the cost of sequencing genes
   c. The rise of Genome-Wide Association Studies (GWAS). A GWAS screens the genome of many hundreds to thousands of subjects in a case-control study or a population-based cohort study. It will screen with > 500,000 SNPs followed by a simple association analysis between the phenotype of interest & all of the genetic markers. The GWAS will then identify the genetic markers associated with the phenotype at a certain statistical significance.
8. There will be a shift from an emphasis on disease treatment to health maintenance.

V. DNA Polymorphisms.
A. A Single Nucleotide Polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide (A, T, C, or G) in the genome differs between individuals or between paired chromosomes in an individual.
B. The DNA of any two people is 99.9% identical.
C. International HapMap Project.
   1. About 10 million SNPs exist in the human population. Of these, more than 5 million have been identified.
   2. Sets of SNPs close together tend to be inherited as a block.
   3. A "haplotype" is this pattern of SNPs in a block (region of a chromosome).
   4. The goal of the project was to develop a haplotype map of the human genome which would describe the common patterns of human DNA sequence variation.
   5. 4 populations were sampled: Nigerian, Japanese, Chinese, and U.S. (Northern/Western Europe ancestry). A total of 270 people were tested.
   6. The project revealed that a smaller set of 300,000 to 500,000 variants can serve as a proxy for the roughly 10 million common genetic variants in the human genome.
   7. This smaller set can now be used in GWAS studies to find the genetic bases of common diseases. This lead to the first gene found for AMD (CFH).
D. The 1000 Genome Project (started January 2008)
   1. An International Consortium was formed to sequence the genomes of at least 1000 people from around the world.
   2. This project will produce the most detailed map of human genetic variation to support disease studies. It will be 10-fold better than the HapMap.
E. Genes, Environment, & Health Initiative (GEI).
   1. NIH began funding the GEI program in late 2007.
   2. This research will help us understand genetic contributions and gene-environment interactions in common diseases.

VI. Molecular optometry.
A. Clinical optometry is undergoing a fundamental, revolutionary transformation.
B. This will change the way optometrists:
   1. Classify diseases
   2. Understand disease
   3. Diagnose diseases
   4. Treat & manage diseases.
C. Look at the patient through a "genetic lens" (i.e., incorporate genetic thinking & principles).
1. Using this lens effectively means rejecting the notion of normality & embracing the idea of variation. The changing paradigm of medicine is framed around individual variability rather than the distinct separation between "normal" and "abnormal."
2. Every patient is an individual & there is infinite variation on the spectrum of health & disease.
3. The clinician should take into account the complex interrelationships among genes, along with each patient’s protein profile, environmental experiences & exposures.
4. We should no longer regard the human body & the visual system as a biological machine in which the OD acts as a mechanic when the parts break down. The clinician’s challenge is to understand the variability of the genetic & environmental factors that lead to disease, develop a prevention plan, and, if necessary, a treatment plan based on the patient’s unique variability.

VII. Improved classification of diseases.
A. The present system is based on clinical description (phenotype).
B. Knowledge from the HGP & other advances will allow a more rational classification based on genetic causes (genotype) and influences.
C. Ex. Retinitis pigmentosa
   1. This is a group of retinal dystrophies.
   2. It includes autosomal dominant (AD), autosomal recessive (AR), X-linked recessive (XR), and mitochondrial forms of inheritance.
   3. It results from mutations on at least 10 chromosomes (48 loci; 37 genes).
D. Ex. Corneal dystrophies (At least 14 genes have been identified on 12 chromosomes)

VIII. Improved understanding of pathogenesis/pathophysiology.
A. We are moving toward a molecular level of understanding of diseases & conditions.
B. Twin studies yield heritability estimates for a number of ocular traits
   1. Cataracts: nuclear 48%; cortical 58% (In other words, genetics accounts for about 48% of nuclear cataract variability & about 58% of cortical cataract variability)
   2. Myopia: 90%
   3. Central corneal thickness: 95%
   4. Intraocular pressure: 63%
   5. Optic nerve head disc area and cup area: 80%
C. Ex. The Glaucomas.
   1. Glaucoma is the 2nd leading cause of blindness in the U.S.
   2. The prevalence of open-angle glaucoma (OAG) in the U.S. in people over 40 years old is ~2%.
      a. Prevalence increases with age (e.g., 0.9% for people 43-54 years old; 4.7% for people over 75 years old).
      b. Black subjects have about 3-5 times the age-adjusted prevalence of OAG compared to whites.
   3. There is about a 10-fold increase in risk for first-degree relatives of glaucoma patients. This is due to genetics and means that you should screen relatives of your glaucoma patients (i.e., cascade genetic screening).
   4. The glaucomas can be inherited as autosomal dominant (e.g., JOAG, pigment dispersion), autosomal recessive (e.g., congenital glaucoma), & multifactorial (most adult-onset types of glaucoma – e.g., POAG, LTG, XFG) forms.
   5. Identification of genes for the glaucomas.
      a. Myocilin (MYOC) accounts for 8-62% of JOAG & 3-5% of POAG.
      b. Optineurin (OPTN) accounts for about 17% of familial NTG.
      c. WDR36 perhaps accounts for 5-17% of POAG or is a modifier gene (for severity?).
      d. CYP4501B1 accounts for about 85% of familial & 25-33% of sporadic cases.
      e. LOXL1 accounts for up to 99% of exfoliation syndrome glaucoma (XFG).
      f. At least 9 other genes have been identified & at least 22 chromosomal loci have been found.
6. Exfoliation glaucoma (also known as pseudoexfoliation glaucoma).
   a. XFG is the commonest cause of secondary glaucoma. It affects about 12% of all glaucoma patients in the U.S. & its prevalence varies by ethnic group.
Table 1. Prevalence of exfoliation glaucoma in different populations

<table>
<thead>
<tr>
<th>Location</th>
<th>Age</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eskimos (Greenland)</td>
<td>&gt; 60</td>
<td>0%</td>
<td>Forsius, 1988</td>
</tr>
<tr>
<td>America (FES)</td>
<td>52-85</td>
<td>1.8%</td>
<td>Hiller et al., 1982</td>
</tr>
<tr>
<td>South India</td>
<td>≥ 40</td>
<td>3%</td>
<td>Thomas et al., 2005</td>
</tr>
<tr>
<td>Singapore Chinese</td>
<td>≥ 40</td>
<td>0.2%</td>
<td>Foster &amp; Seah, 2005</td>
</tr>
<tr>
<td>Malay</td>
<td></td>
<td>4%</td>
<td>Shen et al., 2008</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>≥ 40</td>
<td>9.3%</td>
<td>Summanen &amp; Tonjum, 1988</td>
</tr>
<tr>
<td>Iceland</td>
<td>≥ 50</td>
<td>10.3%</td>
<td>Jonasson et al., 2003</td>
</tr>
<tr>
<td>Greece/Crete</td>
<td>≥ 40</td>
<td>16.1%</td>
<td>Kozobolis et al., 1997</td>
</tr>
<tr>
<td>Australia (Aborigines)</td>
<td>&gt; 60</td>
<td>16.3%</td>
<td>Taylor et al., 1977</td>
</tr>
<tr>
<td>Middle Sweden</td>
<td>65-74</td>
<td>18%</td>
<td>Ekstrom, 1987</td>
</tr>
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</table>

b. SNPs in the gene LOXL1 account for most of the XFG cases. The population attributable risk in various studies was 99% (Iceland/Sweden), 88% (Iowa), & 71% (Utah).

c. The risk of pts carrying 2 copies of the high-risk SNPs is about 700 times the risk of pts carrying 2 copies of the low-risk SNPs and about 2.47 times the population average risk.

d. The product of the gene modifies elastin fibers that are a major part of exfoliation syndrome (XFS) changes.

e. Testing for LOXL1 variants is available.

D. Ex. Age-related macular degeneration.

1. Introduction.
   a. AMD is the most common cause of blindness in the elderly in the Western world.
   b. Its prevalence is 0.05% before the age of 50 and 11.8% after the age of 80.
   c. 1st-degree relatives of patients with AMD have a 4.2 times increased lifetime risk of late AMD.

2. CFH gene.
   a. A polymorphism in the complement factor H gene (CFH) on chromosome 1q31 accounts for 20-50% of the overall risk of developing AMD.
   b. This polymorphism is the Y402H variant (Tyr402His; i.e., a tyrosine to histidine substitution at amino acid 402) due to a 1277T-C transition in exon 9 (SNP = rs380390) of the gene.
   c. Individuals who carry a single copy of this variant have a 2- to 4-fold increased risk of AMD.
   d. Individuals who carry two copies of the variant have a 5- to 7-fold increased risk.

3. LOC387715/ARMS2 (Age-Related Maculopathy Susceptibility 2) & a secreted heat shock serine protease HTRA1 (High Temperature Required Factor A-1) gene.
   a. The LOC3877715/ARMS2 & HTRA1 genes are extremely close to each other on chromosome 10q26, & polymorphisms in them account for as high as 57% of the overall risk of developing AMD.
   b. Individuals who carry a single copy of this variant have a 3-fold increased risk of AMD.
   c. If a patient were homozygous for risk alleles at both CFH and LOC387715HTRA1, the disease odds ratio (OR) would be about 58.

4. Complement Factor B (CFB) & Complement Component 2 (C2) genes
   a. Variants of these genes can confer a significantly reduced risk of AMD & other variants can increase the risk. CFB is a complement activating factor.
   b. For example, the odds ratio for a protective polymorphism in the CFB gene is 0.36 and in the C2 gene is 0.45.
   c. Analysis of the CFH, CFB, and C2 variants can predict the clinical outcome in 74% of AMD pts & 56% of controls.

5. Other complement-related genes.
   a. SNPs in the C3 gene, on chromosome 19q13, increase the risk of AMD 1.8-fold for 1 risk allele or 2.4-fold for two risk alleles.
   b. One study implicated a C7 SNP (rs2876849) as being protective for AMD.
   c. A SNP variant (rs2511989) in the SERPING1 gene encoding the complement component 1 (C1) inhibitor may also be involved.
6. A risk model has been generated based on 5 variants of the CFH, LOC387715/HTRA1, CFB, C2 genes.
   a. About 1% of the population has high-risk homozygotes at all loci. This confers about a 250-fold increase in risk for AMD.
   b. About 10% of the population has a 40-fold increase in risk.
   c. This is compared to patients carrying the lowest risk genotypes at all loci (about 2% of the population).

7. A newer risk model has been generated using variants of the CFH, LOC387715, C2, C3, & CFB genes, age (≥ 70), smoking, BMI, education, & baseline AMD grade. Using a cutoff risk score of -1.5, this model has a sensitivity of 83% and a specificity of 68% for progression to advanced AMD. This is comparable to the Framingham risk score prediction model for coronary heart disease (CHD).

8. A polymorphism in the mitochondrial genome (A4917G) apparently confers an increased risk for AMD (OR = 2.16). This missense mutation occurs in subunit 2 of the mitochondrial NADH dehydrogenase (Complex 1).

9. Innate immunity and inflammation in general and complement overactivation in particular appear to play a central role in AMD pathogenesis.

10. The new data suggest new targets for early intervention & predictive DNA testing as a future option. It may also lead to the development of new biomarkers for the disease. The future challenge is to develop risk models incorporating gene-gene interactions, gene copy-number variations, epigenetics, environmental interactions, treatment effects, and clinical covariates.

IX. Improved diagnostic testing.
   A. Microarrays (DNA chips, RNA chips, Protein chips)
   B. “Lab-on-a-chip” microfluidics
   C. Point-of-care testing
   D. Tests will become available in the next 10 years to determine risk for common diseases.
   E. Types of genetic tests.
      1. Molecular genetic test – tests for a genetic condition by testing for nucleic acid (DNA or RNA)
      2. Cytogenetic test – tests for anomalies of number or structure of chromosomes. This type of testing includes karyotyping & FISH analysis (fluorescent in situ hybridization).
      3. Biochemical genetic test – test to study enzymes, proteins or metabolites that may be altered by a genetic condition.
   F. Thinking will shift to probabilities (statistical risks) instead of definitive answers.
   G. Goal of $100 genome sequencing. The cost of sequencing the first genome (HGP) was about $3,000,000,000. Knome will sequence your whole genome for $99,500 or just your 20,000 genes for $24,500, and Illumina will sequence your whole genome for $48,000. Recent approaches in development for reading genomes have resulted in a drop in cost to about $5,000, and suggest that a $100 human genome may come as soon as 2012.
   H. Some currently available tests for ocular diseases:
      1. arRP-1 sequencing array (U. of Michigan) for mutations causing autosomal recessive forms of RP
      2. ABCR (ABCA4) gene mutation detection assay (Asper Ophthalmics) for mutations causing Stargardt disease
      3. LCA microarray test for Leber congenital amaurosis (Asper Ophthalmics)
      4. More than 1700 genetic tests available from commercial labs (including tests for various glaucomas, corneal dystrophies, retinal dystrophies, cataracts, AMD, & various pathogens)
      5. The Carver Nonprofit Genetic Testing Laboratory (Univ. of Iowa) (www.carverlab.org) offers relatively cheap testing with fairly fast turn-around times for 17+ ocular diseases.
   I. Reasons for genetic testing.
      1. Predictive testing: offered to asymptomatic individuals with a family history of a genetic disorder
         a. Presymptomatic testing for predicting adult-onset disorders (e.g., Huntington disease)
         b. Susceptibility (predispositional) testing for estimating risk of developing adult-onset disorders (e.g., breast cancer)
      2. Diagnostic testing of a symptomatic individual: used to confirm or rule out a known or suspected genetic disorder in a symptomatic individual
      3. Carrier testing: used to identify patients who have a gene mutation for a disorder inherited in an autosomal recessive or X-linked recessive manner. This kind of testing is offered to patients who have family members with a genetic condition, family members of an identified carrier, or patients in ethnic or racial groups known to have a high carrier rate for a particular disorder.
Table 2. Examples of ethnicity-based carrier screening

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ethnic group</th>
<th>Carrier frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary hemochromatosis</td>
<td>Northern European</td>
<td>1/8</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>European</td>
<td>1/25</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>1/46</td>
</tr>
<tr>
<td></td>
<td>African</td>
<td>1/60-65</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1/150</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Black</td>
<td>1/14</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Ashkenazi Jewish</td>
<td>1/12</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Ashkenazi Jewish</td>
<td>1/26</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>African/Asian/Mediterranean/Middle Eastern</td>
<td>Varies with population</td>
</tr>
</tbody>
</table>

4. **Prenatal diagnostic testing**: offered when there is an increased risk of having a child with a genetic condition, e.g., due to maternal age, family history, ethnicity, or suggestive marker screen or fetal ultrasound examination.

5. **Newborn screening**: used to identify individuals who have an increased chance of having a specific genetic disorder so that treatment can be started as soon as possible.

6. **Preimplantation genetic diagnosis (PGD)**.
   a. This involves in vitro fertilization (IVF) followed by genetic diagnosis before implanting the cells. This offers an alternative to prenatal diagnosis or termination of affected pregnancies.
   b. This technique has already been used in the case of monogenic diseases (e.g., retinoblastoma) and chromosomal aberrations.

X. **Improved management and treatment**.
A. **Identification of patients with susceptibility genes** will allow determination of:
   1. Risk level
   2. Types of testing/treatment
   3. Timing of surveillance visits
   4. Appropriate lifestyle changes

B. **Assessing benefits/harms**. This can be done in three stages.
   1. **Analytic validity**. This is the ability of a genetic test to accurately & reliably measure the genotype of interest. This is usually high for genetic tests.
   2. **Clinical validity**. This is the ability of a genetic test to accurately & reliably predict the clinically defined disorder or phenotype of interest. This is harder to demonstrate due to low or unknown disease penetrance, and the fact that population diversity and bias can lead to an overestimation of the disease susceptibility conferred by a SNP. It involves clinical sensitivity, clinical specificity, prevalence of the disorder, positive & negative predictive values, penetrance, and modifiers (gene or environmental).
   3. **Clinical utility**. This is the improved measurable outcomes shown by a genetic test, and the usefulness and added value to patient management resulting from a test compared to current patient management without genetic testing. The magnitude of benefit depends on the availability & effectiveness of preventive or curative therapies or on the ability to avoid potentially harmful interventions in the case of negative test results. For example, at-risk children who test negative for retinoblastoma would avoid the potential harms of general anesthesia.

C. **Gene therapy**.
   1. China has approved the world’s first commercially-licensed gene therapy (October, 2003). It is an injectable medication (Gendicine) using an adenoviral vector to deliver a p53 tumor suppressor gene for head-and-neck squamous cell carcinoma.
      a. Adeno-associated viral vector was used to deliver normal copies of the RPE65 gene to the retina via subretinal injection.
      b. Visual function & structural recovery have been shown in a canine model of Leber congenital amaurosis (LCA).
   c. Phase 1/2 clinical trials on humans have begun in the U.S., England, and Israel.
   3. **Two ocular angiogenesis human trials** have been done.
      a. They involved intravitreal injection of a viral vector with a gene for pigment epithelium-derived factor (PEDF) in patients with severe AMD. PEDF is an antiangiogenic factor.
      b. One clinical trial was Phase 1 and the other trial was Phase 2.
4. **Ciliary neurotrophic factor (CNTF)** for human retinal degeneration.
   a. Encapsulated cell technology (ECT). Human RPE cells genetically engineered to produce human CNTF are placed in implants (1-mm dia.) with semipermeable polymer outer membranes with 15-nm pores. The implants prevent the attack by the host immune system. The implants are surgically implanted into the vitreous.
   b. Phase 1 clinical trial has been completed. ECT was used to deliver CNTF to 10 pts with RP. The trial indicated that it was safe & that 2-3 lines of improved VA were noted in 3 of 7 eyes.
   c. Phase 2/3 trial for early-stage RP ongoing
d. Phase 2/3 trial for late-stage RP ongoing
e. Phase 2 trial for atrophic AMD ongoing

D. **Antisense drugs**.
   1. These drugs are complementary strands of portions of messenger RNA (mRNA).
   2. The drugs bind to mRNA and inhibit transcription of the protein.
   3. Fomivirsen was the first antisense drug marketed (1998). It is used for treating CMV retinitis.
   4. A 2nd-generation antisense inhibitor, iCo-007 (iCo Therapeutics Inc.), targets C-raf kinase mRNA & is in phase I clinical trials for treating retinal neovascular diseases like diabetic retinopathy. This drug may prevent the growth of new blood vessels and inhibit increased vascular permeability by decreasing the production of C-raf kinase through which multiple growth factors (e.g., VEGF) signal.

E. **RNA interference (RNAi)**.
   1. Small double-stranded interfering RNAs (siRNAs) can silence messenger RNAs carrying a complementary sequence.
   2. RNAi is used to selectively inhibit gene expression in various diseases, including infectious diseases, cancer, inflammation/immune dysfunction, CNS disorders, and cardiology.
   3. RNAi drugs for AMD.
      a. Quark Pharmaceuticals has started phase 2 clinical trials of **PF-4523655**, an siRNA molecule that silences the hypoxia/oxidative stress-inducible gene RTP801. This inhibits CNV & is anti-apoptotic & anti-inflammatory.
      b. Allergan has stopped a phase 2 trial of AGN211745 (Sirna-027) which silences the vascular endothelial growth factor (VEGF) Receptor-1 gene. Poor phase 2 results were the reason.
      c. Opko Health, Inc. has terminated its phase 3 clinical trial of bevasiranib (Cand5) which silences the VEGF gene. The COBALT study involved a combination of bevasiranib & Lucentis therapy, but it was deemed unlikely to meet its primary end point.

F. **Complement-targeted therapeutics for AMD**.
   1. **Complement component inhibitors**:
      a. Potentia Pharmaceuticals has successfully finished a phase 1 trial for wet AMD using intravitreal injections of **POT-4**, a drug that binds to & inhibits complement factor 3 (C3).
      b. Ophthotech has started a phase 1 trial using intravitreal injection of **ARC1905**, an aptamer-based C5 inhibitor, for wet AMD. A phase 1 trial for dry AMD is planned for 2009.
   2. **Receptor antagonist**: Jerini Ophthalmics, Inc. is in pre-clinical stages of testing **JPE-1375** (an antagonist for the C5a receptor) for dry AMD.

G. **Other anti-inflammatory treatments for AMD**.
   1. Jerini Ophthalmics, Inc. has started phase 1 trials for wet AMD using intravitreal injection of **JSM-6427** (an antagonist of integrin α5β1 receptor). This will inhibit ocular angiogenesis, inflammation, & fibrosis.
   2. Othera Pharmaceuticals has begun phase 2 trials for dry AMD using **OT-551 eye drops**. This is a free radical scavenger that also targets inflammatory pathways.

H. **Genetic counseling** – new role for primary care clinicians (including optometrists)
   1. Genetic counseling will become more and more a primary care responsibility.
   2. There are not enough genetics counselors or medical geneticists to handle the increase in demand.
   3. Every health care provider will become a genetic counselor in the next 10 years.

XI. **Pharmacogenetics / Pharmacogenomics**.
   A. Each year, 100,000 people die from adverse reactions to drugs & over 2 million have serious reactions.
   B. Some drugs work well in some patients & not as well in other patients.
   C. DNA variations (polymorphisms) in genes responsible for drug metabolism affect a patient’s response to drugs.
D. **Variants (SNPs, insertion/deletions, & copy-number variations)** in genes that are involved in drug metabolism, drug transportation, drug targets, & intracellular signaling pathways can account for much of the ability of some drugs to cause adverse reactions and/or to be ineffective.

E. The **Amplichip CYP450 Microarray** (Roche/Affymetrix) is now commercially available for testing two of the genes involved in drug metabolism (CYP2D6 & CYP2C19). This test accounts for ~99% of known poor and ultra-rapid metabolizer genetic variation in these genes.

F. Suggestive studies in eye diseases
   1. Response to intravitreal bevacizumab (Avastin) was significantly worse for the risk-conferring CFH Y402H CC genotype compared with the TC and TT genotypes.
   2. In Age-Related Eye Disease Study (AREDS) patients, treatment with zinc plus antioxidants vs. placebo resulted in a reduction of 68% in progression to advanced AMD for patients homozygous for the non-risk-conferring CFH Y402Y TT genotype, but only an 11% reduction in progression to advanced AMD for patients homozygous for the risk-conferring CFH Y402H CC genotype.
   3. SNPs in the prostaglandin F(2alpha) receptor gene correlate with a response to latanoprost (Xalatan) treatment in normal subjects. They may be an important determinate of variability in response.

G. ODs will prescribe medications and determine drug doses based on the patient's genotype and SNP pattern:
   1. Improving efficacy & safety of drugs
   2. Decreasing morbidity & mortality
   3. Decreasing overall cost of health care.

H. "Personalized medicine" will evolve for many drugs and diseases by the year 2020.

XII. **Ethical, legal, social implications** (ELSI).
   A. Informed consent
   B. Confidentiality/privacy
   C. Discrimination (e.g., employers, insurers)
   D. Psychological impact
   E. Fairness in access to genetic services
   F. Conceptual/philosophical/religious implications
   G. Clinical issues including education of clinicians, patients, & the general public

XIII. **Why the genomics revolution is important for optometric practice.**
   A. Virtually all diseases have a genetic component. This means optometric physicians will need to:
      1. raise genetic hypotheses with every patient (i.e., look at each patient through a "genetic lens")
      2. realize when genetic factors play a role in a patient. Thus, we will have to be aware of genetic contributions to the common diseases seen in practice
      3. improve family history taking skills and, in selective cases, draw a three-generation pedigree
      4. be able to identify patients who need genetic services and/or referral
      5. know how, when, and where to obtain advice and refer patients
         a. Find a genetic counselor in your area by using the Website of the National Society of Genetic Counselors (http://www.nsgc.org).
         b. Find a medical geneticist in your area by using the Website of the American College of Medical Genetics (http://www.acmg.net).
         c. Identify patient support groups for specific conditions by using the Website of the Genetic Alliance (http://www.geneticalliance.org).
      6. know how to access new knowledge on medical genetics and use it in patient care
   B. Everyone has 5-50 significant genetic flaws.
   C. There is an exponential rise in genetic knowledge.
   D. New diagnostic/prognostic/treatment options are increasing. This means optometric physicians will need to:
      1. learn the indications for genetic testing and the availability of genetic tests for specific ocular conditions.
      2. deal with “risk” and genetic predisposition
      3. manage low and moderate risk patients
      4. use genetics to individualize patient care and preserve health
      5. be able to read the increasing number of ophthalmic journal articles on genetic/genomic issues, and thus to keep current
      6. be able to identify, understand, and address the ethical, legal, social, and financial issues associated with genetic conditions as they arise in primary and specialty (e.g., pediatric optometry and low vision) practice
   E. There are not enough genetic specialists to handle the increase in demand.
F. There is a growing demand for genetic information and services by patients. Thus, optometrists will need to be able to:
   1. address the increasing number of patient’s questions and concerns about new genetic technologies and information related to eye care
   2. explain genetic concepts

G. Direct marketing of genetic tests to health care professionals & potential customers is occurring.
   1. decodeme.com – For $985 they will take a buccal sample and genotype ~1,000,000 of your SNPs. Their report will give you your risk for 42 diseases & traits (including AMD and XFG) as well as trace your ancestry.
   2. 23andme.com – For $399 they will take a saliva sample and genotype ~550,000 of your SNPs. Their report will give you your risk for 115 diseases & traits (including AMD) as well as trace your ancestry.
   3. cyGene Direct’s Glaucoma & Macular Degeneration DNA Analysis ($99.95).
   4. ArcticDx for $750 will process a saliva sample (Macula Risk) and claim that they will determine your risk of developing AMD by checking for polymorphisms in the CFH, C3, & ARMS2 genes & in the mitochondrial gene MTND2. They also include age and smoking history.
   5. Many of the directly marketed tests are unregulated & unvalidated.
   6. Nutrigenetic testing. Some companies say they can use genetic information to develop an individualized diet plan. Such tests may be misleading or even harmful. They tend to make claims that can’t be proven scientifically.

7. Direct-to-consumer (DTC) genetic testing has raised concerns about:
   a. The potential for inadequate pretest decision-making
   b. Misunderstanding of test results
   c. Access to tests of questionable clinical value
   d. Lack of necessary follow-up
   e. Unexpected additional responsibilities for primary care providers.

H. National Ophthalmic Disease Genotyping Network (eyeGENE).
   1. Created by NEI in partnership with 10 CLIA-approved laboratories
   2. Register on-line at their Website
   3. Submit the patient sample (blood draw & shipping are the only costs).
   4. You receive the report.
   5. The referring OD must ensure that the patient receives genetic counseling before & after.
   6. eyeGENE goals:
      a. to facilitate research into genetic causes of ocular diseases
      b. to provide accurate diagnostic genotyping to patients with inherited eye diseases
      c. to identify, engage, & enhance patient recruitment for therapeutic clinical trials
      d. to provide a repository of DNA coupled to de-identify phenotypic info for researchers.

I. Enhanced genetic literacy & competency of ODs is necessary.

J. What you can do now.
   1. Start learning about genetics & eye diseases (see references below).
   2. Read & start working on “Recommended Core Competencies in Genetics for Doctors of Optometry (http://www.opted.org/i4a/pages/index.cfm?pageid=3400). These competencies have been endorsed by the American Academy of Optometry, the American Optometric Association, & the Association of Schools & Colleges of Optometry.
   3. Identify patients that could benefit from gene testing.
      a. Many disease genes are available for testing now.
      b. A number of CLIA-certified labs can perform these tests (e.g., eyeGENE)
   4. Identify patients for studies & clinical trials.
      a. eyeGENE
      c. PubMed

K. Two quotes from Edwin M. Stone, MD, PhD, are instructive (Arch Ophthalmol 2007;125:205-12):
   1. “We can reasonably expect the deployment of useful tests for nearly all inherited eye diseases during the next 5 to 10 years.”
   2. “In 1990, it may have been true that the rate-limiting steps of genetic testing for rare eye diseases were mostly in the laboratory. However, in 2006, the most rate-limiting steps in the translation of genomic information from the laboratory to the clinic are to inform clinicians about the availability of these tests and to educate them about their proper use and interpretation.”

XIV. Selected References.
A. Books.

B. Journal articles.
29. Wormington CM. How to put genetics into your practice now. Rev Optom 2004;141(11).

C. Selected Websites
1. Disease specific information for health care professionals
   d. RetNet (Retinal Information Network): http://www.sph.uth.tmc.edu/Retnet/
2. Genetic tests
   c. The John & Marcia Carver Nonprofit Genetic Testing Lab: https://www.carverlab.org/
3. Family history tools
4. Directories of clinical genetics specialists
5. General genetics resources
   a. National Human Genome Research Institute: http://genome.gov/Education/
   b. Genetic Science Learning Center: http://learn.genetics.utah.edu/
   c. Genetics Education Center: http://www.kumc.edu/gec/
   e. National Coalition for Health Professional Education in Genetics (NCHPEG): http://www.nchpeg.org