I. INTRODUCTION

If you think you have seen dramatic technological changes in the last five years, just watch the next five!

Regarding the access to an incredible amount of genetic information it has been said that “even if we do not know and do not want to know, we now know that we can know”…and, “choosing not to know can be as heavy a burden as choosing to know”.

Scenario: two people meet and are considering whether or not to consider developing a relationship….so, they exchange hairs and say to each other, “call me if you think we should date again.

Picture a multi-handicapped person saying, “why would my parents choose to let nature take its course instead of having genetic testing with the technology available today?” Will the day come when we shall see a wrongful LIFE lawsuit?

“The human genome is becoming a substitute for the soul”….Alex Mauron

There have been several cartoons published regarding genomics and humorous situations. See Figure 1.

This course will instruct optometrists how to recognize genetic disorders like Smith-Magenis Syndrome, Diabetes, and cancers, and what can be done to prevent or treat these conditions, as appropriate.
There are several goals and objectives for this course on Genomics for the Practicing OD including:

- To Develop a Better Understanding of the “New Genetics” (termed “Genomics”)
- To Understand the Effects of the Environment on the Genetic Apparatus
- To Review a Number of Diseases and Disorders Already Identified by Genetic Testing that Affect the Eye and Visual System
- To Appreciate the Impact Genomics Will Have on the Future of Optometric Practice and the practice of all the other health professions

CASE PRESENTATION: Vision Training Patient in the Pediatric Clinic with Smith-Magenis Syndrome

Figure 2: A pediatric patient with Smith-Magenis Syndrome
(photo used with permission of the family)

The patient is a vision therapy patient in our clinic as a referral from a pediatrician for vision therapy for learning disorders and visually-related problems. The patient had been previously diagnosed with ADHD and was receiving medication for it. Despite this, there were reportedly multiple developmental delays. According to her teacher, this patient had trouble focusing, with eye movements for reading, and with visual information processing.

Objectively, the patient was testing for visual-motor and non-motor perceptual delays. Deficits were found in all areas of the Test of Visual Perceptual Skills (TVPS), namely visual discrimination, memory, spatial relations, form constancy, sequential memory, figure-ground and visual closure. See Figure 3.
The Beery Visual-Motor Integration (VMI) test showed delays in copy forms accuracy and speed. See Figure 4.

The patient was originally diagnosed as having Down Syndrome (Trisomy 21) but signs and symptoms during routine health care delivery by the pediatrician made for suspicions that there was another diagnosis rather than Down Syndrome. The patient underwent genetic studies at a local laboratory to see if there could be any clarification of the diagnosis. The various genetic studies are performed by a simple cotton-tipped applicator “cheek swab”. In short, a cotton-tipped applicator is twirled between the cheek and upper teeth and gums and sent to the laboratory for analysis...similar to any police detective sending cells from under the fingernails of a victim who has scratched an assailant! These cells are stable without refrigeration or other preservative care for years and years so no special care of the specimen is required. In fact, the swab is simply placed in a standard envelope and mailed to the laboratory. The results are shown in Figure 5.
Figure 5: Cheek swab genetic testing results for this patient.
Note the deletion of short arm of Chromosome 17 Band p11.2

Genetic testing on the cells derived from the “cheek swab” confirmed that the patient has Smith-Magenis Syndrome. The following is a brief overview of this syndrome:

- Features – Squared face, upslanting eyes that are deep-set, prominent forehead and mid-facial hypoplasia
- Cognitive and Adaptive Problems
- Motor Delay and Coordination Problems
- Mild to Moderate Mental Retardation
- Hyperactive, Inattention, Impulsive, and Temper-Tantrums
- During Infancy there are Feeding Problems, Sleep Problems, Hypotonia and Often “Failure to Thrive”
- The Disorder is due to a Deletion of short arm of Chromosome 17 Band p11.2

The patient has very dedicated, well-off and loving parents who want only the best for their child and therefore they make certain that she is a faithful VT patient for her optometric care. The patient also enjoys support from her pediatrician and from all her other health care professionals including a child psychologist. All these health care professionals believe that her vision therapy program has helped tremendously as she demonstrated good, steady progress in motor skills and general behavior with the implementation of Vision Training. See Figure 6.
The patient continues to do well and has only mild intellectual disability, so she is advancing in her schoolwork, and only a couple years behind what she should be for her age.

**NOW IT IS TIME TO BEGIN THE PROCESS OF TRANSFERRING OLDER THINKING ABOUT GENETICS TO THE NEW THINKING ON GENOMICS.**

- The theoretical Life Expectancy is 120 Years as proven by studies on the normal Human Cell
- Ancient Writings State that Life Should Be 120 Years
- Fact….Males Only Live About 75 Years and Females About 80 Years on Average
- Question…Where Did the Other 40-40+ Years Go???

I have “preached” POLYGENICS for Years! This means that genetic predisposition + environmental insults leads to the manifestation of virtually every disease and disorder that affects humankind, In the past this was MOSTLY Speculation but now the Human Genome Project has proven the polygenic concept to be FACT!

In 1900 the three leading causes of death were pneumonia, tuberculosis and diarrhea. Today, the major causes of death are cancer, heart disease, stroke, injuries, lung disease, diabetes, influenza and kidney disease (in that order). Public Health measures were largely responsible, with a minor role of newly invented medications, for this shift. Life expectancy in 1900 was 46 years. Today in the United States, it approximates 80 years for women, and 75 years for men, with women outliving men on the average approximately five years.

However, the theoretical maximum life expectancy is 120 years according to studies on normal cellular biology and physiology. It appears quite possible that through control of the environment and better understanding and use of genetic information that life expectancy may continue to dramatically increase in the near future. How long each of us, and our offspring, will live will depend more and more on understanding how the environment, including the genetic code of organisms that attack our bodies, interacts
with each of our own individual genetic code composition and adversely affects cell and organ survival and effect total body life expectancy.

Just as we consider the health care practice at the time of our grandparents to have been primitive, so will our grandchildren feel about today’s optometry and the overall health care delivery to today’s population. They will say, for instance, you mean the treatment for cancer was with poisons and not genetic manipulation to eliminate these abnormal cells called cancer!!!

In 2003 the 50th year celebration occurred for the discovery of the structure of DNA by Rosalind Franklin, James Watson and Francis Crick. See Figure 7.

![Figure 7: Double-helix structure of DNA](image)

In the same year, the completion of the sequencing of all 3 billion base pairs of the human genome was completed. Now the newly trained geneticists are undertaking a new basis for genetic research that will have far-reaching effects on the clinical practice of optometry, as well as all the other major health professions, with all the legal and ethical issues that will emerge as a result of these new discoveries. The next big research steps will be the discovery of the function of all these sequenced genes and how they affect health and longevity.

It is interesting to note that each and every one of us, that is all human beings, have approximately 5-50 significant genetic defects. The good news is that for the most part, these do not seem to be all that significant clinically. However, these genetic abnormalities lead to shortening of the theoretical life expectancy by manifesting diseases such as diabetes, hypertension, cancer, auto-immune diseases, etc.

It is important to grasp the conceptual differences between the previous thinking in terms of “old genetics” versus “new genetics”. In “old genetics” the thinking was that diseases are the result of a mutation in a single gene, a missing chromosome or an extra part of a chromosome. In “new genetics” it is recognized that in actuality, that virtually all medical conditions, trauma excepted, have a genetic component that is multi-factorial, meaning that a number of genes interact with a number of environmental factors leading to disease(s). The term for genetic predisposition for a disease and it then being activated by an environmental influence is termed “polygenic”. In short, a genetic predisposition plus an environmental insult (viral infections, medications, ultraviolet light, food additives, artificial sweeteners, etc.) results in a specific disease being manifested.
Because many of these genetically predetermined diseases, triggered by an environmental interaction, affect the eye or are primarily manifested in the eye, this will definitely impact optometric practice in the future.

A. There are four (4) different kinds of genetic disorders – Single Gene (Mendelian or Monogenic), Multi-factorial (complex or polygenic), Chromosomal and Mitochondrial. There are currently over 1000 DNA-based genetic tests available for clinical and research uses. All involve the faulty production of proteins because of ribosomal defects. See Figure 8.

**Figure 8: Production of faulty amino acids, leading to defective proteins, by defective DNA and RNA. These genetic defects are often on many genes.**

1. **Single Gene Disorders** – These are caused by changes or mutations that occur in the DNA sequence of one, single gene. There are about 6,000 known single gene disorders and these occur in about 1/200 births. Single Gene Disorders may be autosomal dominant, autosomal recessive and X-linked. Examples include cystic fibrosis, sickle cell anemia, Marfan Syndrome, etc.

2. **Multi-factorial (or Polygenic)** – here the disease or disorder is caused by a combination of factors leading to mutations in multiple genes. Further, the impact of the environment on the genetic apparatus is the key in making genetic predisposition to a disease becoming manifested. The bottom line is that genetic predisposition plus environmental insult equals the onset of a disease or disorder. The classic example for disease in this genetic disorder is Diabetes Mellitus Type 1.

In Type 1 Diabetes Mellitus, there is a genetic predisposition due to a defect in the genetic apparatus. If a person with this predisposition develops a certain viral infection, usually an influenza virus or the mumps or measles virus, this results in activation of a clone of “T” cells that should only neutralize and get rid of the virus. However, in the genetically predisposed patient the result is an attack by these “T” cells on the Beta Cells of the Pancreas resulting in destruction of the Beta Cells. The Beta Cells produce insulin and therefore with destruction of these cells there is a lack of insulin that results in the development of Diabetes Type 1.

In this type of genetic disorder, it is theorized that genetic predisposition and environmental insult leads to virtually all the diseases and disorders that develop and affect all of mankind.
3. **Chromosomal** – Chromosomes are carriers of genetic material and thus missing components or extra copies of components can lead to diseases and disorders. For example, in Down syndrome the patient has three copies of chromosome 21 and the resulting clinical manifestations of Down syndrome, i.e., mental retardation, ocular disorders, cardiac disorders, etc., are due to this “extra” genetic material.

4. **Mitochondrial** – This is considered rare at this time and is due to mutations in the non-chromosomal DNA of mitochondria.

B. Geneticists are specialists in evaluating a person’s DNA and diagnosing genetic disorders

1. This is an incredibly hot area now for research and clinical services.
2. New genetic tests are coming out literally weekly.
3. There are an incredible number of issues surrounding the use of this information for ethical reasons including how insurance carriers will utilize this information in determining insurability, insurance rates, etc. will be utilized. The manipulation of the genetic apparatus and choosing off-spring with certain physical attributes such as eye color, height, etc. may be possible in the near future. Perhaps genetic studies will be ordered in choosing a spouse in order to insure that offspring will be more “normal” when brought into this life!

4. There are multiple Web Sites to help practitioners of all types, including optometry, to utilize genetic information in the care of patients.

5. Use any Search Engine, i.e., Google, etc., and go to Genetics, Genome, Genetic Diseases, etc. and you will find thousands of resources instantly available for your use in furthering your knowledge on this subject.

6. This presentation is based on the use of multiple web-sites, published articles, books and, especially the Human Genome Project Website.

C. There are over 1000 genetic tests, all are DNA-Based Tests, currently available for diagnosing pathological conditions occurring in humans.

1. Currently it is thought that there is not “adequate” regulation for genetic testing in that virtually anyone can order genetic testing
2. However, most insurance companies may not pay for such testing and the testing is expensive
3. Actual clinical use is still somewhat debatable for many of these tests due to cost-effective issues and concerns over how to use the results of genetic testing in the clinical care of patients
4. Current testing is available for a host of diseases and disorders including testing for Disease Carrier Screening, Pre-implantation Genetic Testing, Prenatal Diagnostic Testing, Newborn Screening, Pre-symptomatic Testing, Confirmation Testing, and, lastly, Forensic/Identity Testing
5. Definitely more research and clinical testing is needed before most of these tests and new tests on the horizon will be widely accepted for clinical use in the care of patients
II. THE HUMAN GENOME PROJECT (see Figure 9)

![Diagram of genome-related areas]

**Figure 9: The hope of the human genome project**

A. This is a US Government led effort to map the entire human genome

1. The project was begun in 1990 and the estimated time to completion was 15 years
2. However, it was completed in only 13 years, in 2003, with the determination of the 3 billion chemical base pairs that make up human DNA
3. Use of the information is to improve genetic data analysis, transfer related technologies to the private sector, including the health care industry, and address ethical, legal, and social issues that arise from the project

B. Clinical testing now available for over 1000 diseases and disorders with many being related to the eye including glaucoma, corneal dystrophies, macular degeneration, retinitis pigmentosa, etc. See Figure 10.

![Image of a corneal dystrophy]

**Figure 10: Genetic corneal dystrophy resulting in leukocornea**
C. New research in this area has led to a continuing explosion of new information and clarification of diseases and disorders many of which have clinical applications in the optometric practice.

III. **OLD, TRADITIONAL CONCEPTS OF GENETICS**

A. Belief of a single gene mutation or missing/extra chromosome leading to a disease or disorder

B. It was believed that most of these diseases and disorders as a result were rather uncommon

C. Therefore, there was very little if any role for the practicing OD or general medical practitioners in the use of this information. One example is Down Syndrome (trisomy 21). See Figure 11.

![Figure 11: Trisomy 21 (Down Syndrome) genome and patient. Notice 21st chromosome triplet, and patients low-set ears and epicanthal folds](http://en.wikipedia.org/wiki/Down_syndrome)

IV. **NEW CONCEPTS OF “GENOMICS”**

A. Utilizes knowledge and technology derived from the Human Genome Project

B. Accepts the fact that virtually all diseases and disorders have a genetic component

C. The concept of “multi-factorial” etiology of diseases and disorders due to genetic predisposition and environmental triggers or influences

D. All health care providers are to be involved in the use of this new information in the clinical care of patients

E. The US Government has recommended that all health care providers be up-to-date in this regard and be prepared to care for patients using “genomic”
information for preventing, diagnosing and treating a host of diseases commonly seen in the practitioner’s specific health care practice

F. Soon each individual’s own genetic code will be imprinted on an Identification Card with all the ethical, social, moral, etc. ramifications yet to be determined and already concerns are being expressed for how this will be used by employers, insurance companies, prospective spouses, planning for having children, etc.

V. BASIC CONCEPTS OF THE NEW MOLECULAR GENETICS

A. The following is a basic review of DNA in the human cell which consists of about 3 Billion base pairs of the four nucleotide bases

1. DNA makes up the genes that make up the chromosomes in the human cell
2. DNA itself consists of a variable sequence of four nucleotide bases labeled A, T, C, and G that are the “letters” of the genetic code. A is for Adenine, T is for Thymine, C is for Cytocine and G is for Guanine.
3. Humans have approximately 20,000 genes spread out over the chromosomes (NOTE: the Fruit Fly has about 14,000 and a worm has about the same as humans at about 20,000 and corn has 50,000!!). All these genes tell cells how to make proteins.
4. Each chromosome consists of one double-stranded DNA molecule and associated proteins
5. Each human cell has 22 pairs of autosomal chromosomes and one pair of sex chromosomes which are either XX (female genotype) or XY (male genotype)

B. Review of the four nucleotide bases of A, T, C and G which are the letters representing the genetic code. See Figure 12.

![Figure 12: DNA base pairs](image)

1. DNA is illustrated by a right handed double helix with about 10 nucleotide pairs per helical turn
2. Each spiral strand is composed of a sugar phosphate backbone and attached bases
3. Each spiral strand is connected to a complementary spiral strand by hydrogen bonding between paired bases
4. The paired bases in DNA are abbreviated A, T, C, and G for Adenine, Thymine, Guanine and Cytosine
5. These bases are repeated millions of times throughout a genome
6. The whole human genome has some 3 billion pairs of these bases
7. The particular order of these determines whether an organism is human, animal, yeast, rice (or another vegetable), fruit fly, etc. as each has its own particular genome. See Figure 13.

![Figure 13: Differences in genotype create differences in phenotype](Image)

C. The following is a review of the “genetic flow of information” being from DNA to RNA to protein synthesis

1. The first process is termed “transcription” and involves the use of the genetic code within DNA to synthesize messenger RNA (mRNA)
2. The second process is termed “translation” and involves the use of encoded information in the mRNA to make proteins. See Figure 14.

![Figure 14: Transcription and Translation](Image)

3. Most of the DNA, about 98%, is involved with coding for various RNA molecules or is directly involved in controlling the expression of the genetic information
4. Only about 2% of DNA is involved in encoding the mRNA to make proteins.
5. DNA transfers information to mRNA in the form of a “code” which is defined by a sequence of nucleotide bases.
6. During the synthesis of the body proteins, ribosomes move along the mRNA molecule and “read” the sequence three nucleotides at a time (the codon).
7. Each amino acid is specified by the mRNA’s codon and then pairs with a sequence of three complementary nucleotides carried by a particular tRNA (the anticodon).
8. RNA is constructed from four types of nucleotides and therefore, there are 64 possible triplet sequences or “codons”.
9. Three of these possible codons specify the termination of the polypeptide chain and are termed “stop codons” and, therefore, 61 codons specify only 20 different amino acids: Alanine, Phenylalanine, Lysine, Cysteine, Glycine, Leucine, Aspartic Acid, Histidine, Methionine, Glutamic Acid, Isoleucine, Proline, Threonine, Glutamine, Valine, Arginine, Tryptophane, Serine and Tyrosine.
10. Most amino acids are represented by more than one codon.
11. A “transcriptome” is the complete set of RNA transcripts present at a given time.
12. A “proteome” is the complete set of proteins expressed by a genome in a cell at a given time.
13. Proteins are the molecular machines of the human cell that do most of the work that is necessary for life.
14. The genome is constant cell to cell, however, the proteonome dynamic and varies by cell type and function.
15. “Proteomics” is the future of this field and clinical diagnosis and treatment as it is the basis for allowing the monitoring of changes in expression of proteins in the presence of normality and diseased states of the cells.
16. Proteomics has led to and will lead to many, many more diagnostic tests based on the protein markers of diseases.
17. NOTE: THE FUNCTION OF MOST OF THE DNA REMAINS UNKNOWN AT THIS TIME!

D. Chromosome locus nomenclature for the 22 pairs of autosomal chromosomes and the two sex chromosomes.

E. The proteome is the complete set of proteins expressed by a genome.

F. All humans have 99.9997% of their DNA sequences identical but there still remains millions of nucleotide sequences for allow for uniqueness.

G. The mouse and humans share 90% of the same genes!

VI. GENOMICS AND THE CLASSIFICATION, DIAGNOSIS, TREATMENT OF DISEASES AND DISORDERS.
A. The new genomics leads to an improved classification of diseases and disorders

B. New discoveries will lead to new and better forms of treatment

C. Earlier and more accurate diagnosis is and will be increasingly possible

D. Prevention of various diseases and disorders may be possible by determining who is at risk with pre-disease screening

E. The understanding of pathologic mechanisms is and will become even clearer

F. Use in carrier screening, predictive testing, prenatal testing, newborn screening, diagnostic testing and forensic testing will become routine in clinical practice

G. Gene therapy for preventing and treating, even curing, diseases is now on the horizon and being utilized on a limited basis

H. Pharmaceuticals will be designed to target individual genotypes and be able to treat diseases and disorders, hopefully, without any side-effects or adverse medication reactions

VII. REVIEW OF SOME SYSTEMIC DISEASES AND DISORDERS AND THE NEW GENOMICS

It is currently believed that most diseases have their very basis pre-existing within the genome. These diseases become clinically manifested due to the proteins they encode. Currently it is thought that over 4,000 diseases stem from mutated genes inherited from one’s parents and that the interaction of the environment on the inherited genetic apparatus with a predisposition to certain diseases is responsible for disease becoming clinically manifested with their specific signs and symptoms.

A. Heart and Blood Vessels Disease -- Case Presentation

The vascular diseases are the most common diseases known to mankind with Atherosclerosis (lay term is “hardening of the arteries”) being fare and away the most common and lethal. Atherosclerosis is the primary underlying etiology for both heart attacks and strokes. Combined, heart attack and strokes cause the death of individuals in developed countries more than any other disease process including cancer.

The vascular diseases are the most common diseases known to mankind with Atherosclerosis (lay term is “hardening of the arteries”) being fare and away the most common and lethal. Atherosclerosis is the primary underlying etiology for both heart attacks and strokes. Combined, heart attack and strokes cause the death of individuals in developed countries more than any other disease process including cancer.
The basic pathologic lesion is the ATHEROMA that is an elevated, fibrofatty plaque (primarily cholesterol) which begins on the tunica intima of the artery. It will progress to involve the tunica media and with time is at high risk to cause problems due to obstruction of the lumen or complications at the site of the atheroma.

What are these problems or complications at the site of an atheroma?

a. Occlusion - when the obstruction reaches about 70% it can begin to interfere with blood flow and lead to ischemia of the tissues it supplies.
b. Calcification - this is the "hardening" referred to in the lay term hardening of the arteries.
c. Ulceration - the surface tends to ulcerate and the necrotic and degenerating material to float on downstream which also may cause problems as "emboli"!
d. Thrombosis on site - this is especially true with ulceration as it is a focal point for clot formation due to the loss of endothelial covering. Thrombosis can instantly lead to a 100% obstruction and an acute problem like heart attack or stroke!
e. Emboli formation - clotted blood, calcified tissue, cholesterol, etc. can embolize from the site of an atheroma.
f. Spasm - these lesions can somehow "irritate" the vessel and result in smooth muscle contraction. Again, this can dramatically increase the obstruction!!
g. Hemorrhage into the plaque - with degeneration the vessels to the tissue of the plaque itself can rupture and bleed into the plaque dramatically increasing the size and increase the obstruction!!
h. Aneurysm formation - due to weakening of the vessel wall so the pressure causes it to balloon out and it may even rupture.

Optometric presentation of hyperlipidemia includes patients who present with premature arcus senilis and lid xanthomas. See Figure 15.

![Figure 15: Arcus senilis and eyelid xanthoma, both potential signs of hyperlipidemia.](image)

Hyperlipidemia can lead to atherosclerosis. Posterior segment signs include lipemia retinalis and central retinal artery occlusion (CRAO). See Figure 16.
Patients with atherosclerosis can also have central/branch retinal vein occlusion (BRVO) and who have a history of hypertension or a metabolic disease such as diabetes mellitus or thyroid abnormalities, etc. are at higher risk for development of atherosclerosis. The aorta and other arteries begin to show evidence of atherosclerosis during childhood, and with the standard American diet, this slowly progresses over the years to be severe by age 80 or so.

The associated genetic predisposition for developing “premature” atherosclerosis is especially found on chromosome 19 and involves the following:

1. APOA 1 and ABCA1 – Encodes apolipoprotein A-1 and promotes HDL (high density lipoprotein) which is good!
2. APOB – Encodes apolipoprotein B which promotes LDL (low density lipoprotein which is bad!
3. APOC2 – Encodes the protein component of VLDL (very low density lipoprotein), which is bad!
4. OLR1 – Encodes oxidized LDL receptors which is bad! Oxidation of the LDL’s rapidly increases the rate of damage that these molecules do in regard to developing atherosclerosis

B. Diabetes Mellitus

Diabetes Mellitus is a major health care problem in developed countries. In fact, there are 1.7 million newly diagnosed cases of Diabetes in the USA each year and 25,000,000 Americans with diagnosed Diabetes Mellitus. It is estimated that there are an additional 58 million people with “pre-diabetes” in the USA! By the year 2020 it is estimated that 33% of the US population will have diabetes. Care for these patients accounts for one-sixth of the total health care dollars expended in the United States of America and by the year 2020 it is expected to be 1/3 of the total health care dollar expenditure. In 2002, the most recent extensive survey available for this type of information,
the direct/indirect medical costs was $132 billion (US) including the accounting for the cost of lost productivity. It has been estimated that 11 million (26.9%) of Americans 65 years and older are diabetic. There are approximately 800,000 newly diagnosed cases of diabetes each year! See figure 17.

Figure 17: Subtle Cotton-wool spots (left) and less-subtle neovascularization (right) in uncontrolled diabetes mellitus

Type 1 Diabetes Mellitus (Juvenile Onset)

Juvenile-onset diabetes mellitus has well-defined associated gene abnormalities:

1. There are about 10 loci identified so far in the human genome that confer “predisposition” to developing Type 1 Diabetes
2. The two getting the most attention is on chromosome 11 and is termed IDDM2 and on chromosome 7 a loci for glucokinase (GCK) which modulates insulin secretion
3. The mechanism appears to be that in a “predisposed” individual in the face of an environmental insult produces antigens that attach to the surface of beta cells in the pancreas which leads to their being killed by CD8 T Lymphocytes
4. The most recent discovery is a gene mutation called SUMO-4 that leads to predisposition of Type 1 Diabetes
5. The HLA (Human Lymphoctyic Antigen) is a powerful regulator of Immunity and is intimately involved in the immune system “wipeout” of the Beta Cells of the Pancreas when an environmental insult “triggers” activation in a genetically predisposed individual
6. Apparently, in the presence of SUMO-4 gene in the face of certain environmental insults, the cytokine production (chemical messengers in the immune system) directs an increased immune response to destroy the Beta Cells of the Pancreas by encoding a protein that modifies the activity of NFeB (an important regulator in cytokine production)
7. The IFIH1 variant gene supports the fact that a viral infection destroys the Beta Cells of the Pancreas as it encodes an enzyme
called interferon-induced helicase that plays a role in the anti-viral immune response.

C. Diabetes Type 2 (Adult-Onset)

Type II DM has many genes affecting disease onset and manifestations. The genetics may be a predisposition for obesity rather than diabetes per se. Many Type II diabetics are much more poorly controlled than Type I diabetics, and thus all too often have a greater complication rate requiring drastic treatment, as seen in Figure 18.

![Pan-retinal photocoagulation (PRP) in uncontrolled DM, Type II](http://commons.wikimedia.org/wiki/File:Fundus_photo_showing_scatter_laser_surgery_for_diabetic_retinopathy_EDA09.JPG)

**Figure 18: Pan-retinal photocoagulation (PRP) in uncontrolled DM, Type II**


Associated Genes:

1. A large number of genes in various locations are associated with the development of Type 2 diabetes and it is thought that a mutation in several of these must occur before the disease can become manifested.
2. Interaction with the environment is critical in developing Type 2 diabetes with special attention given to weight control and exercise.
3. The genes getting the most attention are the Beta3-Adrenergic Receptor gene and a specific mutation of this gene called TRP64ARG, especially in Native Americans, Hispanics and Blacks.
4. Other genes associated include HNF4A (influences the secretion of insulin in response to a glucose load), FABP2, LpL and PPAR along with a host of others.
5. There is no current genetic testing for Type 2 diabetes as the genes involved are numerous and it requires a number of mutations for development of the disease, however, it will be developed!
NOTE: in both Type 1 and Type 2 Diabetes the best estimate is that ¼ to 1/3 of these patients have NEVER had an adequate eye examination by a qualified examiner, that is, by an optometrist or ophthalmologist!!

D. Hypertension has a large number of genes associated with the onset and severity. These genes are undoubtedly triggered in part by environmental factors such as diet, smoking and stress. Retinal effects can be severe, and make a good argument for routinely screening blood pressure in primary care optometry. See Figure 19.

Figure 19: Grade 3 hypertensive changes of the left retina with AV nicking (AVN) involving the inferior temporal retinal vasculature. Also noted are deep retinal hemorrhages (RH) and flare hemorrhages (FH).

1. There are at least 14 genes associated with hypertension development
2. ADD1 and CLCNKB both are involved with sodium re-absorption and therefore work at the renal level for controlling the amount of salt in the system and lead to excessive intravascular volume leading to hypertension
3. Salt excess and the resulting increased circulating plasma volume is considered to be the major pathway for developing hypertension
4. AGT encodes angiotensinogen and AGTR1 along with AGTR2 both encode angiotensin II receptors
5. CYP11B2 encodes the proteins involved in Aldosterone synthesis
6. EDN1 encodes endothelin-1 which is a powerful vasoconstrictor produced by endothelium and vascular smooth muscle cells

E. Cancer has a very large number of associated genes with many of the specific forms of cancer being diagnosed and therapy guided by genetic testing.
It is well-known that light skinned individuals with excessive sun exposure develop pre-cancerous lesions termed actinic keratosis and, if not treated, are at high risk for basal cell carcinoma. See Figure 20.

![Figure 20: Actinic keratosis (left) and basal cell carcinoma, requiring biopsy for diagnosis](image)

1. **Malignant Melanoma** – Here there is mutation in the MC1R gene observed in people with light-skin and freckles, especially if their hair is red, leads to less protection from ultraviolet light and an increase in free radicals in the skin. The newest and latest recommendation for prevention is to avoid the sun between 10:00 AM and 4:00 PM in sunny environments (like Oklahoma and Southern California) and to stay out of tanning booths! The presentation on the skin is much easier to see in Caucasians than on the retina, as seen in Figure 21.

![Figure 21: Basal cell carcinoma on the skin (left) and retina of a Caucasian patient. Imaging like B-scan ultrasound or MRI along with biopsy will be necessary to diagnose the latter.](image)

2. **Lung cancer** – Abnormal genetic foci described as p53, p16, MYCL1 and FHIT are associated with the development of small cell carcinoma of the lung, especially in the presence of tobacco smoke!

3. **Prostate cancer** – Gene abnormalities known as BRCA 2, NKX3A, PTEN, RBI, p53, p27, p21, PCA3 AND KA11 are all associated with development of this type cancer but to date the associated environmental triggers are not identified.
4. **Breast Cancer** – Gene abnormalities known as BRCA1, BCRA2, HER2, CCND1, p53 and Ras are involved in the development of this type of cancer and somehow estrogen plays a critical role in stimulating predisposed cells for the development of breast cancer.

**NOTE:** THE BCRA 2 GENE MUTATION RESULTS IN AN INCREASED RISK OF CANCER OF THE BREAST IN FEMALES AND OF THE PROSTATE IN MALES! IT HAS LONG BEEN KNOWN THAT THERE IS AN INCREASED INCIDENCE OF CANCER OF THE PROSTATE IN MEN WITH A POSITIVE FAMILY HISTORY FOR A MOTHER OR GRANDMOTHER HAVING HAD BREAST CANCER...NOW WE KNOW WHY!

5. **Leukemia** – There are several gene abnormalities but one has gotten quite a bit of attention is the NF1 gene on Chromosome 17

6. **Colon Cancer** – Abnormality in MLH1 gene due to a mutation is associated with the predisposition for this cancer

7. **Gene abnormalities** have also been identified for lymphoma and many other forms of cancer

F. **Alzheimer Disease** – This disease is linked to Chromosome 19, the Apolipoprotein Gene and the SORL1 Gene. ApoE4 and SORL1 Gene abnormalities both increases the risk for the more aggressive form of Alzheimer’s Disease due to less formation of the normally formed protein and resulting in the formation of a toxic form of a precursor protein to Amyloid. The ApoE2 Gene reduces the risk, and ApoE3 results in intermediate risk. There is a rare form of Alzheimer’s Disease (far less than 1% of cases) which is transmitted as Autosomal Dominant and due to a defect in chromosomes 1, 14 or 21 and is clinically manifested as an early age onset (35+ years of age).

G. Other Genes and Human System Diseases include the nervous system, obesity, lungs (emphysema, etc.) and the ORMDL3 gene is associated with childhood asthma in over 70% of cases, skin (basal cell carcinoma, etc.), connective tissue, personality (novelty seeking, etc.), handedness, male-pattern baldness, alcoholism, tobacco addiction, homosexuality, etc.

**VIII. REVIEW OF SOME OCULAR DISEASES AND DISORDERS AND THE NEW GENOMICS**

A. Adult Onset Primary Open-Angle Glaucoma is associated genes are OPTN (optic neuropathy-inducing protein) and GSTM1.

B. Juvenile Onset Primary Open-Angle Glaucoma is associated with MYOC/TIGR, LMX1B, CYP1B1 and OPTN

C. Normal Tension Glaucoma is associated with OPA1 and OPTN

D. Congenital Glaucoma is associated with CYP1B1
A. NOTE: OcuGene is a genetic test kit for open angle glaucoma that was originally on the market in 2002. OcuGene detects a genetic marker (mt-1) in the promoter region of the glaucoma-related TIGR or GLC1A gene. The test is positive in 15-20% of POAG patients and is associated with the “aggressive” form of POAG, the type that is less responsive to treatment. Testing is 99% sensitive and costs about $250 (wholesale). The OcuGene test does not appear to be commercially-available at this printing (2011), but may be available again for practitioners in the future. See Figure 22.

![OcuGene Test Kit]

Figure 22: Determining glaucoma risk with genetic testing
Source: [http://www.insitevision.com](http://www.insitevision.com)

B. Aniridia is associated with the PAX6 gene abnormality and Wilms Tumor of the kidney. Treatment for the eye is often with a specialty contact lens with an artificial pupil for photophobia. See Figure 23.

![Aniridia Child]

Figure 23: Aniridia often presents asymmetrically, and may be incomplete

C. Corneal Dystrophies, such as Fuchs Endothelial Dystrophy and posterior polymorphous, are associated with COL8A2. Bowman’s Membrane associated Corneal Dystrophies are associated with mutations in the TBFBI Gene with mutations on Exon’s 4 and 12. Meesman’s Corneal Dystrophy is associated with mutations in KRT3 Gene at Exon7 and KRT12 Gene on both Exon’s 1 and 7. Treatment may require penetrating keratoplasty and/or specialty contact lenses. See Figure 24.
CASE REPORT: Child with corneal dystrophy transmitted by a Dominant Gene and genetic testing performed on entire family of mom, dad, seven siblings.

D. Macular Dystrophies are a bit more clearly worked out in some cases such as ELOVL4 and Stargardt’s, HEMICENTIN-1 associated with AMD 1 (Age Related Macular Dystrophy 1), and ABCA4 associated with AMD 2, and the CFH gene is associated with Caucasians producing a different protein which leads to age related macular degeneration. The presentation is much later in life than the young-adult onset of fundus flavimaculatus, now thought to be the same diagnosis as Stargardt disease. The devastating effects on central vision are the same, however. Treatment is low vision devices and genetic counseling. See Figure 25.

E. Retinoblastoma has an abnormal gene locus on Chromosome 13 which is a mutation in the RBI gene and there are multiple labs that perform testing. A white pupil (leukocoria) is often the first clinical sign of this potentially fatal cancer, which often manifests aggressively in children. Treatment is surgical and sometimes requires enucleation. See Figure 26.
Figure 26: Leukocoria is often the ominous first presentation of retinoblastoma

F. Retinitis Pigmentosa (RP) is actually a family of diseases in which the retinal pigment epithelium (RPE) is not able to renew the phagocytized discs from the photoreceptors, and thus clumps and dies. RP has over 100 genes which are active in the rod cells of the retina and in which mutations may lead to its development. There are 3 kinds of RP: autosomal dominant, autosomal recessive and X-Linked in which males are obviously more likely to be affected as males only have one X chromosome. The patient will first manifest symptoms of night blindness (nyctalopia). There is no cure for RP, but its progress can be slowed with 15000 IU of vitamin A palmitate PO QD. See Figure 27.

Figure 27: Classic bone spicule presentation indicating death of the RPE in RP (left) and much more subtle early signs in far periphery (right)

G. Other diseases and disorders

IX. IMPLICATIONS FOR OPTOMETRIC PRACTICE AND OPTOMETRIC EDUCATION

A. There is definitely a need for a “Core Curriculum” in Genomics in the schools and colleges of optometry
1. The National Coalition for Health Professional Education in Genetics has recommended that a Core Curriculum be implemented for all health care providers both independent and dependent.

2. The Core Curriculum is to make certain that all health care providers at a minimum be able to: appreciate their own limitations of their genetic expertise, understand the social and psychological implications of genetic diseases/disorders, and to know how and when to refer to proper professionals trained in genetic diagnosis, treatment and management of genetic disorders.

B. Need for a “Core Continuing Education Curriculum” for CE to practitioners

C. Opportunities for the primary care optometrist as the care of patients will shift from diagnosis and treatment to prevention. Also, patients will demand more “genetic/genomic” information and services to provide them clinically important information.

1) Managing patient’s concerns and expectations
2) Clinical use of Family History
3) Identifying specific genetic conditions related to both the eye and general health
4) Assessing “risk” and managing “risk”
5) Ordering Screening and Diagnostic Genetic Testing
6) Dealing with the ethical, legal, and social implications
7) Providing ongoing primary and secondary care
8) Serving as the “gatekeeper” for specialty referrals
9) Counseling patients and their families to enhance their understanding and helping to make informed decisions

NOTE: It is anticipated that there will be a direct marketing of genomic information to patients via e-mail, telephone, television adds, etc. just as the pharmaceutical industry has over the past few years.

D. Risks to the profession if are not involved

E. Benefits to the patients if all health care providers are current in Genomics and utilize Genomic Information in the care of their patients

X. WHAT CAN WE DO?????

A. Choose our parents better (if we get to do this thing again)

B. Control the controllable factors that affect our life expectancy

C. Proper nutrition and antioxidants, nutritional supplements

D. Work diligently to diminish the adverse effects of the environment on our health by avoiding cigarette smoke, air pollution, food products that are bad for us and anything else considered harmful
E. Stay up-to-date on the subject so that when new tests are available we can use it in order to enjoy better health and a longer life for ourselves, our family members and our patients

END OF PRESENTATION: GENOMICS FOR THE PRACTICING OD