Evolution of Direct-to-Consumer Genetic Testing: Present and Future Markets

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Chief Scientific Officer
Pathway Genomics Corporation
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The Current State of Affairs

- “If we postpone until we have more information, we are not taking advantage of what we know” -- K. Steffansson

- “We all know we are going to die, but don’t worry about it. Why not have the same response to personal genetic information?” -- S. Pinker

- The revolution will have a great impact on the medical community. When a consumer arrives at the doctor’s office to get help interpreting the genomic information, the doctor is likely to respond “What’s a SNP?” -- The Wall Street Journal
How we can use genetics today?

- Take advantage of what we know now – use information to educate, motivate and engage people in the uses of genetics
- These are early days in the clinical utility of genetics in complex diseases
- Report genetically valid results
- Meet/exceed regulatory standards
- Responsible communication/utilization of data
- Education of clients and physicians
- Ensure privacy and security of data

“Ultimately the translation of advances in genomic research to routine patient care will require an educated patient population and educated health care professionals” Feero, Guttmacher and Collins, 2008; JAMA 299; 1351
Translating Genetic Discoveries into Medical Practice

- More and more genetic information will become validated and clinically useful, including gene-gene and gene-environment interactions
- DTC companies can provide comprehensive genetic tests to the general population, with information integrated into a PHR
- DTC genetic companies will translate scientific discoveries for the consumer and the physician and help to provide education on the use of genetic information
- Genetic information will play a critical role in the future of medicine
  - Early prediction of risk coupled with preventative action
  - Early detection of disease combined with targeted therapies
  - Early prevention based on novel therapies developed from genetic discoveries
Personalized Medicine is Making a Difference in the Lives of People

- Kate Robbins
  - Lung cancer
- Doris Goldman
  - Cardiac sudden death
- Jeff Gulcher
  - Prostate cancer
Pathway Genomics, Corp.

- DTC genetic testing company with on-site lab
- CLIA/CA laboratory licenses, high complexity testing
- World class scientific team of MDs, PhDs, Geneticists, Scientists and Bioinformatics
- Custom genotyping chip with broad genomic coverage: Complex disorders, monogenic diseases, pharmacogenetics and ancestry
- Multiple genotyping platforms used with cross validation of platforms
- Family history and lifestyle questionnaires are used to produce a comprehensive picture of disease risk
- Genetic counselors are used – certain genotype results will prompt automatic counseling session
Management and Scientific Team

Jim Plante, President/CEO

David Becker, PhD, Chief Scientific Officer, Geneticist

Michael Nova, MD, Chief Medical Officer

Linda Wasserman, MD, PhD, Dir of Clinical Pathology

Neil Howell, PhD Geneticist

Michael Cox, Chief Privacy Officer

Scott Mednick, Chief Marketing Officer

Chris d’Eon, VP Marketing

Jim Woodman, VP Business Development

Edgar MacBean, VP Product Dev &Mgmt
Scientific Advisory Board

Rudolph E. Tanzi, PhD
Joseph P. and Rose X. Kennedy Professor of Neurology, Harvard Medical School
Director, Genetics and Aging Research Unit, Institute for Neurodegenerative Disease, Massachusetts General Hospital

Christoph Lange, PhD
Associate Professor Department of Biostatistics, School of Public Health, Harvard University
Assistant Professor of Medicine, Harvard Medical School

Hywel Jones, PhD
True Materials
DNA Sciences
Founding team of two gene sequencing companies - True Materials and ParAllele.

Stephen L. Wagner, PhD
Founding Scientist, Neurogenetic Pharmaceuticals
Principal Investigator - University of California San Diego School of Medicine

John C. Reed, MD, PhD
President and Chief Executive Officer, Burnham Institute for Medical Research

Blaine Bettinger, PhD - “The Genetic Genealogist”
The Process at Pathway Genomics

1. Customer picks their kit
2. Customer saliva is collected
3. Customer returns test to lab
4. DNA is processed and analyzed
5. Results are placed on customers secure online account
6. Physician and genetic counselors are available for review of results
Pathway Genomics Saliva Collection Kit

- Pathway Genomics-developed
- Simple, easy saliva collection
- Sample container and shipping device included
Criteria for SNP Selection in Complex Conditions

- Validated marker = primary and secondary confirmation study
- Preliminary research marker = primary study
- **Primary study**
  - Minimum 1000 cases and 1000 controls
  - Ethnic matching
  - p value, OR significant
  - Can use proxy markers LD=1
- **Secondary study**
  - Minimum 500 cases and 500 controls
  - Same ethnicity as primary study
  - Same allele must show association in the same direction
  - OR significant
- All papers reviewed by PhD and/or MD staff
- One SNP selected per gene/region to avoid duplicating a signal
- We will continue to update the panel and odds ratios as more is known
<table>
<thead>
<tr>
<th>Complex Diseases - Currently Reported</th>
<th># of Genes</th>
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<tbody>
<tr>
<td>Age-related macular degeneration</td>
<td>4</td>
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<tr>
<td>Alzheimer's disease, late onset</td>
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<tr>
<td>Amyotrophic lateral sclerosis (sporadic)</td>
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<td>Asthma</td>
<td>2</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>Breast cancer</td>
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<td>Colorectal cancer</td>
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<td>Coronary artery disease</td>
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<tr>
<td>Diabetes, Type 1</td>
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<tr>
<td>Diabetes, Type 2</td>
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<tr>
<td>Glaucoma</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4</td>
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<td>Lung cancer</td>
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<td>Melanoma</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Myocardial infarction</td>
<td>18</td>
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<tr>
<td>Obesity</td>
<td>4</td>
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<tr>
<td>Osteoarthritis</td>
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<tr>
<td>Peripheral arterial disease</td>
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<td>Prostate cancer</td>
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<td>Psoriasis</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>13</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>13</td>
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<tr>
<td>Ulcerative colitis</td>
<td>10</td>
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</table>
Health Conditions: Age-Related Macular Degeneration

HEALTH CONDITIONS

Age-related macular degeneration

Macular degeneration is a common cause of blindness and vision problems among people older than 50 in the United States. This condition also is called age-related macular degeneration, or AMD. AMD damages the macula, a small part of the eye’s light-sensitive retina, the layer of tissue that sends vision signals to the brain. Because the macula is responsible for seeing sharp details directly in the center of the field of vision, damage caused by AMD can interfere with... more about Age-related macular degeneration...

GENETIC RISK | LIFESTYLE RISK | FAMILY HISTORY RISK | POPULATION RISK

Your Genetic Risk Level:
Average Risk

The analysis did not identify any significant genetic risk in your results, and your genetic risk is typical of the overall population.

WILL I GET AGE RELATED MACULAR DEGENERATION?
There is no test that can tell you if you will or will not get this condition, and average genetic risk does not mean you will not get it. Since this is a common disease in people over 75, any preventative measures should be considered to lower your overall risk for macular degeneration.

WHAT SHOULD I DO?
With an average genetic risk, it is still recommended that you follow good lifestyle choices that can lessen your overall risk. Because nearly 30% of the population between 75-85 years of age will have symptoms of AMD, it is important to have routine eye exams and become informed about this disease. We have partnered with Harvard Medical School to provide you with extensive information about macular degeneration.

WHAT WE TESTED FOR & WHY
Click for details on what we tested and why.
AMD: Genetic Details

Age-related macular degeneration

Genetics Overview
Age and smoking are important risk factors for age-related macular degeneration (AMD). Approximately 30% of people 75 years old or over show signs of AMD. Cigarette smoking increases the risk of AMD two- to four-fold. AMD is more common in white populations than in Hispanic or African-American populations. There is also a strong hereditary component to AMD. In studies with twins, it was estimated that 46% to 71% of the variation in the overall severity of AMD is genetically determined.

Like other late-onset diseases, AMD has early-onset counterparts (monogenic macular dystrophies) that are caused by mutations in single genes. For example, Stargardt disease, which is the most common form of inherited juvenile macular degeneration, is caused by an autosomal recessive mutation in the ABCA4 gene. Like other late-onset diseases, AMD is a complex disease that results from the cumulative effect of mutations in many genes.

In the last five years, variants in the two most important genes that increase the risk of developing AMD have been identified and characterized. These two genes are the complement factor H gene (CFH) on chromosome 1 and the HTRA1 gene on chromosome 10. The study of these genes will give scientists clues to the defects that lead to the development of AMD.

Data Table

<table>
<thead>
<tr>
<th>GeneHLA Region</th>
<th>SNP</th>
<th>Your Genotype</th>
<th>Associated Allele</th>
<th>Population Frequency</th>
<th>Odds Ratio</th>
<th>Population Studied</th>
<th>Validated Marker</th>
<th>PubMed ID</th>
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<tbody>
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<td>C2</td>
<td>rs547194</td>
<td>G/T</td>
<td>T</td>
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<td>T</td>
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<td>CFH</td>
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<td>A/C</td>
<td>A</td>
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<td>HTRA1</td>
<td>rs11206538</td>
<td>G/G</td>
<td>A</td>
<td>0.22</td>
<td>1.00</td>
<td>Caucasian</td>
<td>Preliminary</td>
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</tbody>
</table>

Molecular details
Pathway Genomics tests for three genes in the complement system: the Y402H mutation in the CFH gene, the IVS10 mutation in the C2 gene and the R102G mutation in the C3 gene all which increase the risk of developing age-related macular degeneration (AMD). In addition, we also test for a promoter mutation in the HTRA1 gene.
### Recessive Monogenic Disorders Covered by Pathway Genomics

<table>
<thead>
<tr>
<th>Ashkenazi Jewish disorders</th>
<th>Inborn errors of metabolism</th>
<th>Blood disorders</th>
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</thead>
<tbody>
<tr>
<td>Bloom syndrome</td>
<td>3-methylcrotonyl-CoA carboxylase deficiency</td>
<td>Factor XI deficiency</td>
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<tr>
<td>Canavan disease</td>
<td>Biotinidase deficiency</td>
<td>Hemochromatosis</td>
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<tr>
<td>Congenital hypothyroidism</td>
<td>Galactosemia</td>
<td>Hemoglobin C diseases</td>
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<tr>
<td>Cystic fibrosis</td>
<td>Glutaric acidemia I</td>
<td>Hemoglobin E diseases</td>
</tr>
<tr>
<td>Factor XI deficiency</td>
<td>Glycogen storage disease type Ia</td>
<td>Sickle cell diseases</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>HMG-CoA lyase deficiency</td>
<td>Thalassemia - beta</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Medium-chain acyl-coA dehydrogenase deficiency</td>
<td></td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Methylmalonic acidemia</td>
<td>Lysosomal/glycogen storage diseases</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Multiple carboxylase deficiency</td>
<td>Bloom syndrome</td>
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<tr>
<td>Glycogen storage disease type Ia</td>
<td>Phenylketonuria</td>
<td>Fabry disease</td>
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<tr>
<td>Hearing loss, nonsyndromic</td>
<td>Propionic acidemia</td>
<td>Gaucher disease</td>
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<td>Maple syrup urine disease</td>
<td>Tyrosinemia type I</td>
<td>Glycogen storage disease type IV</td>
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<td>Mucolipidosis type IV</td>
<td>Very long-chain acyl-coA dehydrogenase deficiency</td>
<td>Mucolipidosis type IV</td>
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<td>Niemann-Pick disease</td>
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<td>Niemann-Pick disease</td>
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<tr>
<td>Tay-Sachs disease</td>
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<td>Pompe disease</td>
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<td>Tay-Sachs pseudodeficiency</td>
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<td>Tay-Sachs disease</td>
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<tr>
<td>Thalassemia - beta</td>
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</tr>
</tbody>
</table>

- Where established, PGNX covers ACMG recommended mutation panels for monogenic disorders + more
- Cystic fibrosis (CF): 23 mutations recommended by ACMG (covers 94% of Ashkenazi CF mutations)
  - PGNX covers 23 + 70 rare but recurrent mutations
Pathway Genomics Tests for Several Pharmacogenetic Markers

<table>
<thead>
<tr>
<th>Drug Response</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin sensitivity</td>
<td>CYP2C9; VKORC1</td>
</tr>
<tr>
<td>Clopidogrel metabolism</td>
<td>CYP2C19</td>
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<tr>
<td>Abacavir hypersensitivity</td>
<td>HLA*5701</td>
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<tr>
<td>Tamoxifen response</td>
<td>CYP2D6</td>
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<td>Methotrexate toxicity</td>
<td>MTHFR</td>
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<tr>
<td>Statin induced myopathy</td>
<td>KIF6</td>
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<tr>
<td>Statin protection against MI</td>
<td>SLOC1B</td>
</tr>
<tr>
<td>Caffeine metabolism</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Oral contraceptives and thrombosis</td>
<td>Factor V</td>
</tr>
</tbody>
</table>
Ancestry

- 248 Paternal Haplogroups
- 1200 Maternal Haplogroups
- Ancestry Informative Markers
  - ~ 6340 Ancestry Markers
- 1400 Unique Haplogroups
Privacy and Security of Client Data is Critical

**Privacy = Appropriate Use**
*Governed by Customer Privacy Policy*
- Hired a Chief Privacy Officer (CPO)
- Developed transparent summary and full privacy statements
- Created one page summary matrix for easier understanding and compliance
- Website compliance reviews

**Security = Privacy Protection**
*Governed by Internal Information Security Policies*
- Administrative, technical and physical controls in place
- Privacy-trained personnel
- HIPAA/HITECH focused, implementing ISO 27002
- “We treat our facility and information as with ‘data center’ level controls
Pathway Genomics Summary

- Depth and Credibility of Clinical and Scientific Teams, and Advisory Board
- Physicians and Genetic Counselors on Staff
- On Site Laboratory with Federal CLIA / CA State Licenses
- Regulatory Compliance
- 50-90% Lower Cost than other DTC Competitors
- More Genetic Markers Used = Largest # of Disease/Traits Covered
- Custom-designed Chip Containing Numerous Meaningful SNPs
- Custom and Proprietary SNPs assays
- Incorporate use of Family History and Health Questionnaire
- Highly Experienced and Successful Consumer Web Management Team
Genome Genetic Testing can Provide Benefit Now and in the Future

- “It is pretty clear that the public is afraid of taking advantage of genetic testing. If this continues, the future of medicine that we would all like to see happen stands the chance of being dead on arrival” F. Collins (Former Director, National Human Genome Research Center)

- Informed patients will accelerate the pace of change in medical practice
- Some of the information is actionable today
- At the current pace of scientific endeavor more information becomes actionable each week
- Education on the risks, limitations and benefits is necessary for the consumer and the physician
Future of DTC Genetics Markets

- The $1000.00 USD genome will be here by 2010
- The complete exome can be sequenced for ~$500.00 USD
- Genotyping will become cheaper - 100,000 markers for $25?
- DNA sequencing will be used for discovery and validation
- Many more markers will be clinically validated and useful
- Inexpensive genotyping will allow for affordable scans for everyone for the majority of the validated causative and meaningful genetic alterations
- DTC genetics companies have the potential to deliver genetic information to the public on a unprecedented scale
- Genetic information and education with responsible communication can have a dramatic impact on future personalized medicine