A NEW ERA IN MEDICINE

Igniting INOVAtion. Empowering Care.
Better Prevention and Management of Chronic Disease are Critical to Improving Health Outcomes and Lowering Healthcare Costs

A unique medical research institute:

- first fully integrated entity to make “personalized medicine” a reality
- weaving together discovery, commercialization, and application of new personalized diagnostics and therapeutics
- the model for 21st century care that applies the latest knowledge to prevent, delay onset, or cure disease
What is Personalized Medicine?

Genomic Profile / Predisposition / Environmental Risks

- Personal Health / Wellness (Disease pre-emption)
- Interaction with Health Care Provider (Early diagnosis if needed)
- Interventions (Targeted treatment individualized to my molecular profile and that of my disease)
- Post-Disease Management
DECODING THE HUMAN BODY
Misspelling of DNA...
Leads to glitch in RNA...
to glitch in protein
Large-Scale Science

- 4 site NIH Microarray Consortium (funded by 15 NIH institutes at Duke, Yale, UCLA, Stanford, TGen)
- 10 years of experience with Affymetrix platform
- 5 years experience with Illumina
- >60,000 RNA expression profiles run
- >100,000 SNP genotyping arrays run (10k, 50k, 100k, 500k, 1M)
- Software developed with industry to call and analyze genotype data
- Public access data warehousing
- First “Genomics Collaborators”, “Center of Excellence”, and “TransMed” site of Affymetrix
- NHLBI Programs in Genomic Applications
- NEI intramural contract site
- NIH Neuroscience Array Consortium
- NCI funded leukemia catalog
- NIA funded Alzheimer’s disease catalog
- ADNI Consortium hub
- International Autism Genome Project Genotyping Site
- High throughput sequencing (Illumina/ABI)
- ENDGAME Consortium
Sudden Infant Death Syndrome (SIDDT)

SNP-Linkage Software Development

**A. TRUE INTERVAL**
- Location: 6q22.1-q22.31
- Location Score: 8.11
- Number of Autozygous SNPs: 13
- Interval: rs1388219 to rs1321370
- Length: 3.60 Mb

**B. SNPs**
- Location: 9q32-q33.1
- Location Score: 6.18
- Number of Autozygous SNPs: 5
- SNPs: rs1856203 and rs883025
- Length: 1.83 Mb

**C. SNPs**
- Location: 11q22.2
- Location Score: 5.94
- Number of Autozygous SNPs: 8
- SNPs: rs4129255 and rs718891
- Length: 0.75 Mb
High-Throughput Mutation Identification

Testis Specific Protein Y-Encoded Like (TSPYL)

(A) Physical Map 6q22.1-q22.31

<table>
<thead>
<tr>
<th>Accession#</th>
<th>Gene</th>
<th>Location (MB)</th>
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<td>FLJ34503</td>
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<td>NM_001527</td>
<td>HDAC2</td>
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<td>HS3ST5</td>
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<td>FRK</td>
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<td>NM_125729</td>
<td>NT5C2L1</td>
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<td>COL10A1</td>
<td>116.49-116.49</td>
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<tr>
<td>NM_021648</td>
<td>TSPYL4</td>
<td>116.62-116.62</td>
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<tr>
<td>NM_000896</td>
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<td>NM_013352</td>
<td>SART2</td>
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<td>NM_173560</td>
<td>RFXDC1</td>
<td>117.24-117.30</td>
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(B) Truncation from frame shift insertion (457-458insG)

(C) Nucleotide Sequence Insertion

TSPYL

- GCG GAG GCT GAG GCG GAG GTG AAG AGA GGA AAG TGC GCC G TG CCA GTC G TG C G G AG G
- A E A E A E E V K T G K C A T V S A A V A E

- GCG GAG GCT GAG GCG GAG GCT AGA AAG AGA GGA AAG TGC GCC G TG CCA GTC G TG C G G AG G
- A E A E A G G G E D R K V R H R L S S R G Stop

Igniting INOVAtion. Empowering Care.
Cortical Dysplasia with Focal Epilepsy and Autism (CDFE)

Strauss et al.
Unraveling Autism

Dietrich A. Stephan

In this issue of AJHG, Alarcón et al., Arking et al., and Bakkaloglu et al. identify a series of functional variants in the CNTNAP2 gene that unequivocally implicate this gene as causing Type 1 autism in the general population.

Autism Spectrum Disorder (ASD) is a catch-all diagnosis for a set of poorly understood neurodevelopmental disorders that are clinically heterogeneous, with a spectrum of severity, characterized by repetitive self-stimulatory behaviors and communication and socialization deficits. ASD is traditionally diagnosed by the age of 3 years and the severe forms can be accompanied by language regression, seizures, and low measured IQ. The more strict diagnosis of “autism” is made through behavioral testing on the ADOS and/or ADI-R rating systems. The umbrella diagnosis of ASD is truncated through a homozygous loss-of-function mutation in a single family. The mechanism of action of the mutation is likely altered attachment of the axon to the glia via the TAG-1 protein and mislocalization of ion channels at the juxtaparanodal junction leading to cortical dysplasia. This finding is now replicated in a large sampling of the autism population by three groups in this issue of AJHG and places the CNTNAP2 gene as the first widely replicated autism-predisposition gene. Alarcón et al., Arking et al., and Bakkaloglu et al. all describe functional variants (both
Medulloblastoma

• Undifferentiated embryonal neuroepithelial tumor of the cerebellum

• Most common malignant brain tumor in children

• *Frequently metastasizes*

Medulloblastoma Treatment

1. Surgery
2. Usually chemotherapy
3. Craniospinal radiation to prevent metastasis

Surviving patients have poor quality of life due to side-effects of radiotherapy:

• Neurocognitive deficits
• Neuroendocrine deficits
• Hearing loss
<table>
<thead>
<tr>
<th>Probe Set</th>
<th>Gene Name</th>
<th>Average Intensity, Non-Metastatic</th>
<th>Average Intensity, Metastatic</th>
<th>Permutational p-value</th>
<th>Average Fold Difference</th>
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<tr>
<td>1937_at</td>
<td>Retinoblastoma 1</td>
<td>3606</td>
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<td>624_at</td>
<td>GTP-binding protein (RAB3B)</td>
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<td>23</td>
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<td>1611_s_at</td>
<td>Interferon (IFN-gamma)</td>
<td>111</td>
<td>39</td>
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<td>1548_s_at</td>
<td>Interleukin 10 (IL10)</td>
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<td>171</td>
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<td>2042_s_at</td>
<td>c-myc</td>
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<td>36</td>
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<td>885_g_at</td>
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<td>297</td>
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<td>440</td>
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<td>Protein kinase (JNK1)</td>
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<td>Nedd-4-like ubiquitin-protein ligase WWPI</td>
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<td>304_at</td>
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<td>463_g_at</td>
<td>Nuclear factor 1 B3</td>
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<td>1380_at</td>
<td>Keratinocyte growth factor</td>
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<td>140</td>
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<td>Tyrosine kinase (TXK)</td>
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<td>1467_at</td>
<td>Epidermal growth factor receptor kinase substrate (Eps8)</td>
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<td>1127_at</td>
<td>Ribosomal protein S6 kinase 2 (RPS6KA2)</td>
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<td>Heat shock protein 27 (HSP27)</td>
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<td>TINUR= NGFI-B/nur77 beta-type transcription factor homolog</td>
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<td>1216_at</td>
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<td>1511_at</td>
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<td>670</td>
<td>640</td>
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<td>726_f_at</td>
<td>Chorionic Somatomammotropin Hormone Cs-5</td>
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<td>829_s_at</td>
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<td>11495</td>
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<td>239_at</td>
<td>Cathepsin D (catD)</td>
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<td>6098</td>
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<td>Replication protein A 14kDa subunit (RPA)</td>
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<td>1530</td>
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<td>1693_s_at</td>
<td>Tissue inhibitor of metalloproteinases (HUMTIMP)</td>
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<td>191_at</td>
<td>Mucin (MUC8)</td>
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<td>370</td>
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<td>1818_at</td>
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<td>90</td>
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<td>283_at</td>
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<td>2645</td>
<td>4256</td>
<td>0.013</td>
<td>1.61</td>
</tr>
</tbody>
</table>
PDGFRA Blocking Antibody inhibits activation of MEK1/2 and MAPK.
Pediatric ALL – Diagnosis and Treatment

Henry M et al, Submitted
Brown KM et al, In Preparation

TEL-AML1
T-Cell
Hyperdiploid (n>50)
MLL
E2A-PBX
BCR-ABL
Novel, High Risk

T-Cell
Diagnostics and Therapeutics for Complex Genetic Disease:

**How can we cure memory disorders?**

DNA Pooling

**Individual genotyping population 1**

Performance in a verbal recall task

<table>
<thead>
<tr>
<th>25%</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>

**N = 345**

- **KIBRA**
- **CLSTN2**

Top 50% performers vs low 50% performers

Top 25% performers vs low 25% performers

**500K SNP Chips**

- **Candidate SNPs** ($\chi^2$-based)
- **Candidate regions** (sliding window)

**KIBRA**

**CLSTN2**

**Individual genotyping population 2**


First to use >500,000 SNPs to scan the genome
Alzheimer’s Disease
Common Kibra Alleles Are Associated with Human Memory Performance

Andreas Papassotiropoulos,1,3*,† Dietrich A. Stephan,3*,† Matthew J. Huentelman,3 Frederic J. Hoernli,1 David W. Craig,3 John V. Pearson,3 Kim-Dung Huynh,1 Fabienne Brunner,1 Jason Comeaux,3 David Osborne,4 M. Axel Wollmer,1 Amanda Aerni,1 Daniel Coluccia,1 Jürgen Hänggi,1 Christian R. A. Mondadori,1 Andreas Buchmann,1 Eric M. Reiman,3,6 Richard J. Caselli,5 Katharina Henke,1 Dominique J.-F. de Quervain1,2

Human memory is a polygenic trait. We performed a genome-wide screen to identify memory-related gene variants. A genomic locus encoding the brain protein KIBRA was significantly associated with memory performance in three independent, cognitively normal cohorts from Switzerland and the United States. Gene expression studies showed that KIBRA was expressed in memory-related brain structures. Functional magnetic resonance imaging detected KIBRA allele-dependent differences in hippocampal activations during memory retrieval. Evidence from these experiments suggests a role for KIBRA in human memory.

Human memory is a polygenic cognitive trait. Heritability estimates of \( \sim 50\% \) suggest that naturally occurring genetic variability has an important impact on this fundamental brain function (1). Recent candidate-gene association studies have identified some genetic variations with significant impact on human memory capacity (2–5). However, the success of these studies depends upon preexisting information, which limits their potential to identify unrecognized genes and molecular pathways (6, 7).

Recent advances in the development of high-density genotyping platforms now allow for high-resolution whole-exome sequencing within the study sample (population structure) can lead to spurious associations between a genetic marker and a phenotype (11). Therefore, we controlled for genetic background and found no evidence of significant population stratification; the participants’ genetic backgrounds formed one normally distributed cluster (\( P = 0.6 \)) (10, 12). We identified 10 participants as outliers (probability of cluster allocation lower than 25%) and excluded them from the genetic association studies. The remaining population (\( n = 341 \)) was stratified into four groups according to their performance in a verbal memory task which modified the original memory 5-in-high statistical confidence (10). Two SNPs fulfilled these selection criteria and were prioritized for subsequent individual genotyping to exclude pooling-related false positives: rs17070145 and rs6439886. Both SNPs map within genes expressed in the human brain: rs17070145 is a common T \( \rightarrow \) C substitution within the ninth intron of KIBRA (GenBank accession number NM_015238), encoding a neuronal protein, and rs6439886 is a common T \( \rightarrow \) C substitution within the first intron of CLSTN2 (encoding the synaptic protein calsthenin 2) (NM_022131).

Both the KIBRA and CLSTN2 SNPs were also significantly associated with differential human memory performance when we genotyped them individually in Swiss cohort 1 using an independent genotyping technology (10). Carriers of KIBRA rs17070145 T allele had 24% better free recall performance 5 min after word presentation (\( P = 0.000004 \)) and 19% better free recall performance 24 hours after word presentation (\( P = 0.0008 \)) than did noncarriers (Table 1, table S1, and fig. S2). TT and CT genotype groups of rs17070145 were combined because the frequency of the TT genotype was low and because both groups displayed similar memory performance (table S1). SNP rs6439886 yielded similar results; however, the mean difference of memory performance between genotype groups was lower than that of rs17070145 (Table 1 and table S1). Both the 5-min and the 24-hour delayed free recall reflected moderate to high memory dependent on the...
High Hit-Rate with Small Molecules and Peptide Inhibitors (75%)

\[ P=0.0003; \text{ CONT vs. LOW DOSE} \]
\[ P<0.0001; \text{ CONT vs. HIGH DOSE} \]
Science

Researchers at Amnestix have discovered a series of genes, and pathways that play a significant role in memory performance in humans using a strategy called whole-genome association analysis. This is performed by scanning the human genome of individuals with and without a trait or disorder at hundreds of thousands of positions to identify where they systematically differ. The approach is technically and computationally challenging but leads to dramatically more accurate understanding of biological processes underlying common human disorders like cognitive dysfunction.

This study was the first ever to describe scanning the human genetic blueprint at over 500,000 positions to identify cognitive differences between humans.

Using the latest whole-genome
More Genetic Risk Factors

Neuron Report

GAB2 Alleles Modify Alzheimer’s Risk in APOE ε4 Carriers

Eric M. Reiman, 1,2,3,17,18,☆ Jennifer A. Webster, 1,17,18 Amanda J. Myers, 4,5,16 John Hardy, 5,6 Travis Dunckley, 1,17 Victoria L. Zismann, 1,17 Keta D. Joshipura, 1,17 John V. Pearson, 1,17 Diane Hu-Lince, 1,17 Matthew J. Hueneelman, 1,17 David W. Craig, 1,17 Keith D. Coon, 1,17,17 Winnie S. Liang, 1,17 RiLee H. Herbert, 1,17 Thomas Beach, 8,17 Kristen C. Rohrer, 6 Alice S. Zhao, 5 Doris Leung, 7 Leslie Bryden, 6 Lauren Marlowe, 6 Mona Kaleem, 6 Diego Mastroeni, 3 Andrew Grover, 8,17 Christopher B. Heward, 5 Rivka Ravid, 10 Joseph Rogers, 8,17 Michael L. Hutton, 11 Stacey Melquist, 11 Ron C. Petersen, 12 Gene E. Alexander, 13,17 Richard J. Caselli, 14,17 Walter Kukull, 16 Andreas Papassotiriopoulos, 1,16 and Dietrich A. Stephan 1,2,17,☆

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2 Banner Alzheimer’s Institute, Phoenix, AZ 85008, USA
3 Department of Psychiatry, University of Arizona, Tucson, AZ 85724, USA
4 Department of Psychiatry and Behavioral Sciences, University of Miami, Miller School of Medicine, Miami, FL 33136, USA
5 Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, 20892, USA
6 Reta Lila Weston Laboratories, Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London WC1N, 3BG, England
7 Division of Thoracic Oncology Research, St. Joseph’s Hospital, Phoenix, AZ 85013, USA
8 Sun Health Research Institute, Sun City, AZ 85351, USA
9 Kronos Science Laboratory, Phoenix, AZ 85016, USA
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12 Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA
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16 National Alzheimer’s Coordinating Center, Department of Epidemiology, School of Public Health and Community Medicine,
Common sequence variants on 20q11.22 confer melanoma susceptibility

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We conducted a genome-wide association pooling study for cutaneous melanoma and performed validation in samples totaling 2,019 cases and 2,105 controls. Using pooling, we have identified (CDKN2A, ARF, CDK4 and a locus on 1p22), and MCIR has been validated as a gene harboring low-penetration risk alleles.

To identify additional low-penetration risk alleles, we carried out a genome-wide association study (GWAS) involving the pooling of 864 cases drawn from a larger population-based sample of cases (individuals with melanoma) from Queensland, unselected for age at onset (Queensland study of Melanoma: Environment and Genetic Associations (Q-MEGA)), and 864 controls (Q1). Each pool was hybridized to six Illumina HumanHap550 arrays, and SNPs were ranked after accounting for pooling error. The proportion of SNPs with P values from pooling of <0.01 was consistent with what would be expected by chance if there were no true associations. Conversely, at smaller P-value thresholds, there were more SNPs than expected by chance. For example, at the 0.0001 threshold, we would expect to see ~55 SNPs under the null hypothesis of no association, but we in fact observed 90 SNPs, indicating that there were a number of true associations (Supplementary Note online).

Here we focus on only the most significant finding from pooling. The first-ranked (rs17305657, \( P = 2.56 \times 10^{-7} \)) and fourth-ranked (rs4911442, \( P = 2.39 \times 10^{-6} \)) SNPs are 1.5 Mb apart on chromosome 20. Multiple other SNPs in this region showed evidence for association (Supplementary Fig. 1 online). When the pooling results were validated by individual genotyping, concordance was excellent.
More Genetic Risk Factors

**A New Theory About ALS**

A new study of “Lou Gehrig’s disease” singles out 14 genes that suggest what may be happening in the ailment: the dissolution of ‘molecular glue’ that normally makes nerve cells adhere to muscle.

Healthy neuromuscular junction

The connection between the nerve cell and the muscle allows transmission of neurotransmitters that enable normal function.

Junction affected by ALS

The nerve cell retracts and becomes dormant after losing connection to the muscle, causing paralysis.

**Sources:** Translation Genomics Research Institute; the ALS Association

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ALS

Multiple Sclerosis

Age-related Deafness

Bipolar

Parkinson’s Disease

Alzheimer’s Disease

Diabetic Neuropathy

PSP

Melanoma

Addictions

ADNI

Estimated Savings in Prevalence & Costs of AD with Delayed Onset/Progression

DISRUPTIVE INNOVATION

Kleiner Perkins Caufield Byers
Mohr Davidow Ventures
Sequoia Capital
Google
P&G

Mayo
Duke
Scripps
Cleveland Clinic
Harvard Partners
CLIA Diagnostics Lab, GMP-compliant, ISO-certified

Photolithography

Chemistry
# Navigenes Health Compass Test Results

**Jonas Salk | Patient ID: 1234567890 | Gender: M | DOB: 8/20/1965**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Condition</th>
<th>Patient's percentile</th>
<th>Patient's lifetime risk</th>
<th>Average lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Abdominal aneurysm</td>
<td>37% - 44%</td>
<td>2.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>+</td>
<td>Alzheimer's disease</td>
<td>37% - 44%</td>
<td>4.4%</td>
<td>9%</td>
</tr>
<tr>
<td>+</td>
<td>Atrial fibrillation</td>
<td>37% - 44%</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>+</td>
<td>Breast cancer</td>
<td>37% - 44%</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>+</td>
<td>Celiac disease</td>
<td>37% - 44%</td>
<td>0.03%</td>
<td>0.08%</td>
</tr>
<tr>
<td>+</td>
<td>Colon cancer</td>
<td>37% - 44%</td>
<td>4.4%</td>
<td>6%</td>
</tr>
<tr>
<td>+</td>
<td>Crohn's disease</td>
<td>37% - 44%</td>
<td>0.55%</td>
<td>0.58%</td>
</tr>
<tr>
<td>+</td>
<td>Diabetes, type 2</td>
<td>37% - 44%</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>+</td>
<td>Glaucoma</td>
<td>37% - 44%</td>
<td>0.21%</td>
<td>1.1%</td>
</tr>
<tr>
<td>+</td>
<td>Graves' disease</td>
<td>37% - 44%</td>
<td>0.90%</td>
<td>0.55%</td>
</tr>
<tr>
<td>+</td>
<td>Heart attack</td>
<td>37% - 44%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>+</td>
<td>Lung cancer</td>
<td>37% - 44%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>+</td>
<td>Lupus</td>
<td>37% - 44%</td>
<td>0.04%</td>
<td>0.03%</td>
</tr>
<tr>
<td>+</td>
<td>Macular degeneration</td>
<td>37% - 44%</td>
<td>1.1%</td>
<td>3.1%</td>
</tr>
<tr>
<td>+</td>
<td>Multiple sclerosis</td>
<td>37% - 44%</td>
<td>0.77%</td>
<td>0.38%</td>
</tr>
<tr>
<td>+</td>
<td>Obesity</td>
<td>37% - 44%</td>
<td>36%</td>
<td>34%</td>
</tr>
<tr>
<td>+</td>
<td>Osteoarthritis</td>
<td>37% - 44%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>+</td>
<td>Prostate cancer</td>
<td>37% - 44%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>+</td>
<td>Psoriasis</td>
<td>37% - 44%</td>
<td>5%</td>
<td>4.0%</td>
</tr>
<tr>
<td>+</td>
<td>Restless legs syndrome</td>
<td>37% - 44%</td>
<td>4.1%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Your account manager:
Laurie Gomer
(800) NAVI-DOC
Contact your account manager if you need any assistance with anything at all anywhere, anyhow and whatsoever.

Your patient's genetic counselor:
Elissa Levin, M.S., CGC
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Regional Launch

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• 20,000 sq. ft. in CIT building
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