

From: [John West](#)
To: russ.altman@stanford.edu
Cc: [Richard Chen](#); [John West](#)
Subject: Re: USE THIS ONE: my edits/slides v2
Date: Monday, August 20, 2012 6:26:50 AM
Attachments: [Personalis El Camino 20Aug2012 Final.ppt](#)

The Final slides are attached.
I accepted essentially all of Rich's suggestions.
I am printing out a couple of copies to hand them.

John

On Mon, Aug 20, 2012 at 6:15 AM, Russ B Altman <russ.altman@stanford.edu> wrote:
Yes, this is a very important point.

Russ

On Aug 20, 2012, at 6:12 AM, John West wrote:

- > We should also ask about turn-around-time for these tests needed by El Camino.
- > HiSeq-2000 runs take almost 2 weeks, plus sample prep and analysis time. Also queue time if we need to batch up a lot of samples into one HiSeq run.
- > The MiSeq is faster (1-2 days) and much lower capacity, so one run could be a single sample or just a few, but it's cost per base is about 6x.
- > The HiSeq-2500 is faster (also 1-2 days) but at >100Gbases / run, would also need a number of exome samples to fill it, and Illumina is pricing its consumables higher.
- > This may not be an issue, but by comparison, a real time PCR microfluidic card (competitive) solution can be run in a few hours after sample prep.

>

> John West

>

> On Sun, Aug 19, 2012 at 10:28 PM, John West <john.west@personalis.com> wrote:

> If we can all be there a little early, we could discuss how to split up the process of presenting.

> I'll see you in the morning.

>

> John

>

>

> On Sun, Aug 19, 2012 at 10:25 PM, Russ B Altman <russ.altman@stanford.edu> wrote:

> My only worry is that it is a lot of slides. I am hoping we can go through all those slides quickly, so that we can listen to them and their needs. I would limit it to 15 minutes, if possible. The stuff of greatest interest to them is really the last 4-5 slides.

>

> I also favor "genome-guided medicine"

>

> I will also try to get there early.

>

> Russ

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>
>
> On Aug 19, 2012, at 10:22 PM, John West wrote:
>
>> Thanks Rich,
>>
>> This looks fine and I will take a final pass through it in the morning before heading over there.
>>
>> John
>>
>> On Sun, Aug 19, 2012 at 9:23 PM, Richard Chen <richard.chen@personalis.com> wrote:
>> HI John, Russ, my edits, john take or leave as you see fit. This
>> includes stats from Russ.
>>
>> added 3 slides regarding PGx and Rare Pediatric Syndromes
>>
>> slide 12: Under work reported in, do we want to mention New York
>> Times (the Mike Snyder thing which i believe mentioned us), and also
>> the scientific papers that the company is based on (Lancet, Nature
>> Biotech, PloS Genetics, etc)
>>
>> slide 14: Russ, ok with the stats/numbers? please edit/add to this
>> slide as you see fit.
>>
>> I changed order of slides 12-16 (thought it might work better, but you
>> can decide if you like it John)
>>
>> slide 17: I changed title by taking out "progressive"
>>
>> slide 17: changed "Staged development of clinical experience:" to
>> "Staged development of clinical services:"
>>
>> slide 18 changed "broader" to "broad"
>>
>> slide 18 last line: "As the database builds, Personalis & El Camino
>> assess the potential for a broader genome-scale joint diagnostic
>> business" ... sounds like we're building a joint business, is this
>> what you meant? If not I would suggest changing to "As the database
>> grows, Personalis & El Camino jointly assess the potential for a
>> broader genome-scale diagnostic opportunities"
>>
>> BTW, "Genomic Medicine" has been used quite a bit recently... I'm
>> wondering if we should use that instead of "Genome Guided Medicine"?
>>
>> putting kids to bed, will revisit slides afterwards.
>>
>> Also I plan to leave here around 6:30am tomorrow to avoid potential
>> traffic... most likely i'll arrive early (~7:30) so we could talk some

>> in the morning...

>>

>> -Rich

>>

>

>

>

Introduction to Personalis

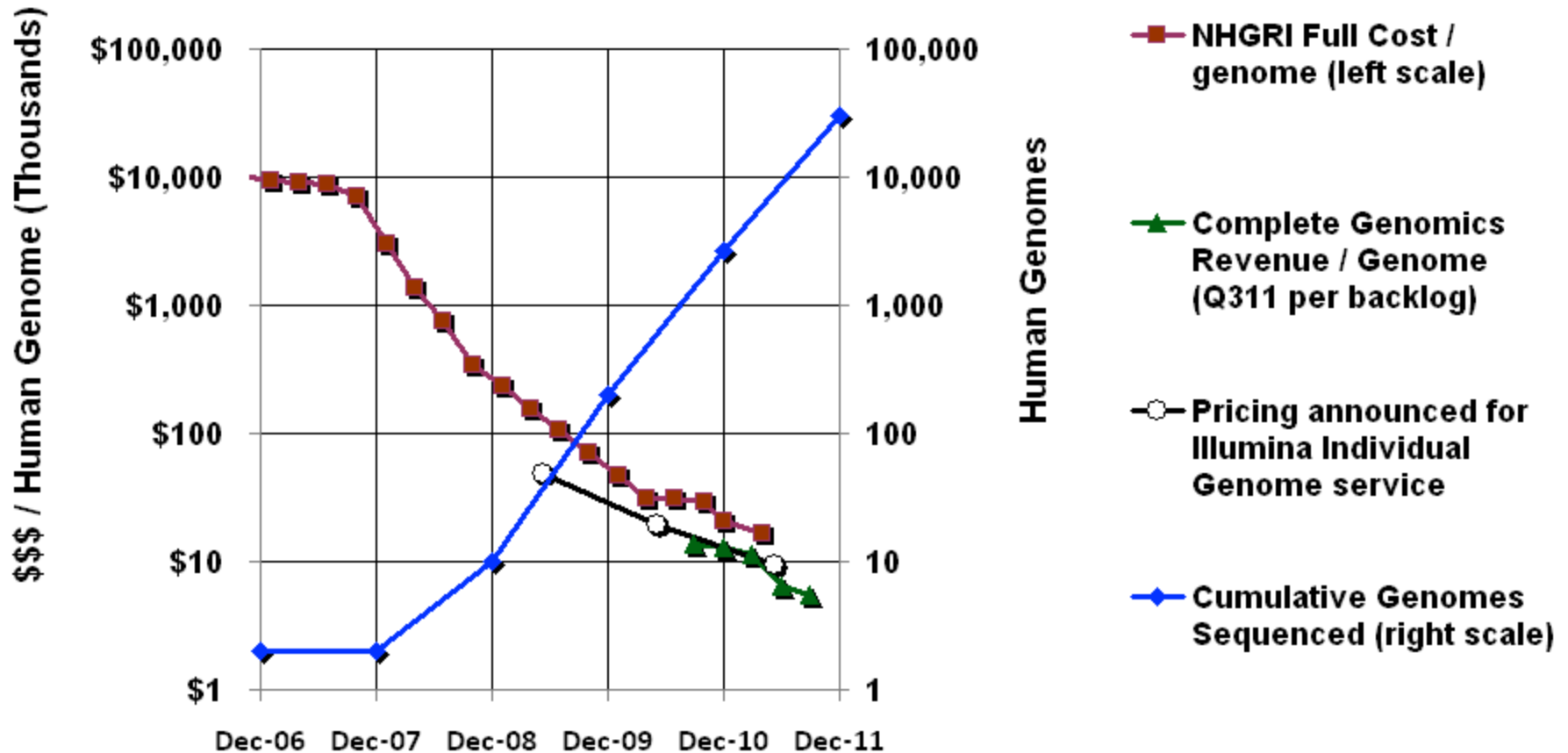
John West, CEO

Richard Chen MD, CSO

Russ Altman MD, Founder (Stanford)

Monday Aug 20, 2012

Rapidly Decreasing Sequencing Costs Drive Exponential Growth in Genomes Sequenced



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The Bottleneck

Interpreting the genome – what does it all mean?



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El Camino Hospital, Leading in Genomics Since 2009

Nov 16, 2009: Sample collection, Illumina whole genome sequencing, family of four.



Genomic Medicine
Institute



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Illumina Announces Its First Full Coverage DNA Sequencing of a Named Family

SAN DIEGO, Apr 16, 2010 (BUSINESS WIRE) --Illumina, Inc. (NASDAQ:ILMN) today announced that it has sequenced the DNA of John, Judy, Anne and Paul West, the first publicly named family to have their DNA sequenced to full coverage by the company. The service was completed in Illumina's CLIA certified and CAP accredited laboratory utilizing Illumina's Genome Analyzer technology and following the established process shown at <http://www.everygenome.com/>.

"We are excited to work with the Wests to produce our first named family DNA sequence," said Jay Flatley, president and CEO of Illumina. "John West has been a leader in this field for almost 30 years, including his tenure as CEO of Solexa prior to that company's acquisition by Illumina in 2007. We're delighted to welcome him back as a customer, and appreciate the vote of confidence in selecting Illumina to provide his family's sequencing. This represents an important step forward for genetic research as sequencing moves from single individuals to full families. More comprehensive information about a family's genetic makeup will lead to greater understanding of the human genome and help physicians make better healthcare decisions for their patients in the future."



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THE LANCET

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient's full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counselling. Genetic analysis included the development of novel methods for the integration of whole genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognised drug responses, and pathogenicity for novel variants. We queried disease-specific mutation databases and pharmacogenomics databases to identify genes and mutations with known associations with disease and drug response. We estimated post-test probabilities of disease by applying likelihood ratios derived from integration of multiple common variants to age-appropriate and sex-appropriate pre-test probabilities. We also accounted for gene-environment interactions and conditionally dependent risks.

Findings Analysis of 2.6 million single nucleotide polymorphisms and 752 copy number variations showed increased genetic risk for myocardial infarction, type 2 diabetes, and some cancers. We discovered rare variants in three genes that are clinically associated with sudden cardiac death—*TMEM43*, *DSP*, and *MYBPC3*. A variant in *LPA* was consistent with a family history of coronary artery disease. The patient had a heterozygous null mutation in *CYP2C19* suggesting probable clopidogrel resistance, several variants associated with a positive response to lipid-lowering therapy, and variants in *CYP4F2* and *VKORC1* that suggest he might have a low initial dosing requirement for warfarin. Many variants of uncertain importance were reported.

Lancet 2010; 375: 1525-35

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See Online/Viewpoint

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N F Neff PhD, Prof R B Altman),

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Department of Pediatrics (A J Butte MD,

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A A Morgan MD), Howard

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K Sangkuhl PhD, J M Hebert MA,

H Sagreya, R Whaley BS,

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M Chou PhD, J V Thakuria,

A M Rosenbaum PhD,

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Groundbreaking publication by Stanford researchers

Identified novel SNP's predisposing to sudden cardiac death, and others guiding pharmaceutical therapy.

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Lancet annotation: Potential advice on hundreds of diseases & drugs.

	Gene name	SNP location	Patient genotype	Drug(s) affected	Summary of effects	Level of evidence
SLC01B1	Solute carrier organic anion transporter family, member 1B1	rs4149056	T/T	HMG-CoA reductase inhibitors (statins)	No increased risk of myopathy	High ³²⁻³⁴
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19	rs4244285	A/G	Clopidogrel and CYP2C19 substrates	CYP2C19 poor metaboliser; many drugs might need adjustment	High ³⁵
VKORC1	Vitamin K epoxide reductase complex, subunit 1	rs9923231	C/T	Warfarin	Reduced dose needed	High ³⁶
CYP4F2	Cytochrome P450, family 4, subfamily F, polypeptide 2	rs2108622	C/C	Warfarin	Reduced dose needed	High ³⁷
ADRB1	β 1 adrenergic receptor	rs1801252	A/A	Atenolol, metoprolol	Might be preferable to calcium-channel blockers	High ^{38,39}
SLC01B1	Solute carrier organic anion transporter family, member 1B1	rs11045819	A/C	Fluvastatin	Good response	Medium ⁴⁰
HMGCR	HMG-CoA reductase	rs17238540	T/T	Pravastatin	Patient might have good response	Medium
HMGCR	HMG-CoA reductase	rs17244841	A/A	Pravastatin, simvastatin	No reduced efficacy	Medium
ADRB2	β 2 adrenergic receptor, surface	rs1042713	A/G	β blockers	Other treatment options might be preferable	Medium ⁴¹
ADRB2	β 2 adrenergic receptor, surface	rs1042714	C/C	β blockers	Other treatment options might be preferable	Medium ^{41,42}
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	rs3892097 rs1800716	C/C	Metoprolol and other CYP2D6 substrates	Normal CYP2D6 metaboliser	Medium ⁴³
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Metformin	Reduced likelihood of response	Medium ⁴⁴
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Troglitazone	Reduced likelihood of response	Medium ⁴⁴

SNP=single nucleotide polymorphism. HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A.

Table 3: Pharmacogenomic variants with summary of effects and level of evidence

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Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence

Frederick E. Dewey¹, Rong Chen², Sergio P. Cordero³, Kelly E. Ormond^{4,5}, Colleen Caleshu¹, Konrad J. Karczewski^{3,4}, Michelle Whirl-Carrillo⁴, Matthew T. Wheeler¹, Joel T. Dudley^{2,3}, Jake K. Byrnes⁴, Omar E. Cornejo⁴, Joshua W. Knowles¹, Mark Woon⁴, Katrin Sangkuhl⁴, Li Gong⁴, Caroline F. Thorn⁴, Joan M. Hebert⁴, Emidio Capriotti⁴, Sean P. David⁴, Aleksandra Pavlovic¹, Anne West⁶, Joseph V. Thakuria⁷, Madeleine P. Ball⁸, Alexander W. Zaranek⁸, Heidi L. Rehm⁹, George M. Church⁸, John S. West¹⁰, Carlos D. Bustamante⁴, Michael Snyder⁴, Russ B. Altman^{4,11}, Teri E. Klein⁴, Atul J. Butte², Euan A. Ashley^{1*}

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Whole genome sequencing of families &
technologies to dramatically improve accuracy

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Performance comparison of whole-genome sequencing platforms

Hugo Y K Lam, Michael J Clark, Rui Chen, Rong Chen, Georges Natsoulis, Maeve O'Huallachain, Frederick E Dewey, Lukas Habegger, Euan A Ashley, Mark B Gerstein, Atul J Butte, Hanlee P Ji & Michael Snyder

[Affiliations](#) | [Contributions](#) | [Corresponding author](#)

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The top two DNA sequencing platforms, analyzing the same person, differ by > 300,000 SNP's and at 70% of insertion & deletion variants. Accuracy is crucial for clinical interpretation.

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August 25, 2011

S10-240+: IO

Exclusive Equity Agreement



EXCLUSIVE EQUITY AGREEMENT

This Agreement between THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY ("Stanford"), an institution of higher education having powers under the laws of the State of California, and PERSONALIS, INC. ("Personalis"), a Delaware corporation, is effective on the 25th day of August, 2011 ("Effective Date").

1 BACKGROUND

Stanford has assignments of certain inventions and has rights to certain trademarks, software, databases and patents. The intellectual property was invented in the laboratories of Dr. Russ Altman, Dr. Euan Ashley, Dr. Atul Butte and Dr. Michael Snyder and is described in the Stanford Dockets listed in Appendix A (the "Stanford Dockets"). Some of this intellectual property was made in the course of research supported by the NIH. Stanford wants to have the intellectual property perfected and marketed as soon as possible so that resulting products may be available for public use and benefit.

Personalis exclusive license to 16 dockets of Stanford IP:
Databases & methods for human genome interpretation

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Scientific / Medical Founders

(Stanford University)



Michael Snyder, PhD

Chair, Department of Genetics
Director, Center for Genomics and
Personalized Medicine



Russ Altman, MD, PhD

Chair, Department of Bioengineering
Director, Biomedical Informatics Program



Euan Ashley, MRCP, DPhil

Director, Center for Inherited
Cardiovascular Disease



Atul Butte, MD, PhD

Asst Professor of Pediatrics (Systems
Medicine) and Medicine (Informatics)

2 Dept. Chairs

3 MD's

1st to publish a
clinical assessment
based on an
individual's genome

Leaders in genetic
analysis technology,
bioinformatics, and
curation.

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Personalis Corporate

- Headquartered in Menlo Park
- No seed financing; direct to \$20.5M Series-A
 - 3 top Sand Hill Road VC firms: Abingworth, MDV, Lightspeed
 - Stanford 10% participation per licensing agreement
- First employees Nov 2011
 - Stanford MD CSO
 - 2 Stanford PhD genetic counselors
 - PhD researchers previously in Stanford founder labs
 - CEO & PhD researchers previously at Illumina
 - Top DNA sequencing platform provider
 - On track for 25-30 employees in 2012, 50-60 in 2013
- Work already reported in:
 - Wall Street Journal & NY Times
 - Technology Review (MIT)
 - Business Week (on-line)
 - Wall Street analyst reports

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Personalis Summary

- Sequencing & serious medical interpretation of human genomes
- Working with the medical system:
 - Physicians, Genetic Counselors, Regulators
- Accuracy at the laboratory level :
 - Rigorous assessment of NGS accuracy, then sample prep improvements
 - Using Stanford-developed methodology reduces the number of variants detected by approx. 700,000 (>20%)
- Accuracy in medical interpretation:
 - Exclusive commercial license to Stanford-developed databases
 - Rigorous QC'ed manual curation of the literature (> 10,000 articles so far)
 - Stanford-developed methodology: 1st to combine multiple risk alleles in complex disease
- Focus on a medical perspective:
 - Reports align with established medical specialties & are designed to work with hospital organizations
- State of the art equipment – Lab & computation

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Pharmacogenomics :

Exclusive Commercial License to PharmGKB™ database



- Personalis' pharmacogenomics service to clinicians focuses on delivering PGx based adverse event, dosing, efficacy reports for over 370 medications
 - These medications span multiple medical fields including cardiology, neurology, psychiatry, anesthesia/pain, oncology, rheumatology etc.
- Personalis PGx analysis is powered by PharmGKB
 - World's leading pharmacogenomics database, began in 2000 at Stanford (Dr. Russ Altman's lab)
 - NIH funded with over \$30M in funding to date, large development effort
 - Personalis has negotiated exclusive commercial license to the database content
 - Over 370 medications with pharmacogenomic data for increased/decreased adverse events, dosing, efficacy
 - Over 60 medications with detailed dose recommendations from CPIC or DPWG

Rare Pediatric Syndromes



- 8 million children a year world wide are born with genetic syndrome (prevalence 1-3%)
- Patients can endure a frustrating series of specific “one-off” genetic tests over years often without yielding a diagnosis (“**Diagnostic Odyssey**”)
- Personalis provides services to enable exome and/or whole genome sequencing for rare variant discovery
- Physicians will be able to submit blood samples from a single patient or trios (patient + 2 parents) for diagnosis

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Rare Pediatric Syndromes

Personalis is uniquely poised to deliver a superior service to clinicians:

- Service developed in conjunction with MD's, scientists, and genetic counselors that understand the key clinical and technical challenges
- Best-in-class pipeline for identifying candidate variants from exome and whole genome sequencing
- Best-in-class, highly accurate proprietary database of disease variants powering our analysis and interpretation
 - Databases (such as HGMD, OMIM) used by other service providers contain significant errors
- State of the art proprietary algorithms
 - For differentiating de novo mutations from sequencing errors
 - For incorporating phenotype information into searches for novel trait associated alleles
 - For identifying true alleles that are IBD
- Ability to interpret variants in intergenic regions, not just exonic regions

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Building towards Genome Guided Medicine

- Solid base in medical genetics research:
 - Continue to build publication base & recognition
 - Experience with large number of genomes
- Staged development of clinical services:
 - Focused tests to meet immediate medical needs in:
 - Pharmacogenomics
 - Rare Mendelian disorders
 - Build towards exome & whole genome
 - Data from early focused tests document the potential for broader benefits of the genome

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Proposed timing, financial & other terms

- Pilot phase prior to Personalis CLIA certification, anticipated early 2013
- Personalis & El Camino define an expanding menu of focused genetic tests, and target test volumes
- El Camino pays just for the tests ordered
- At its own cost, Personalis implements the tests through broad genetic assays (e.g. exome & even whole genome)
 - Delivers focused results to El Camino promptly
 - Builds a database of broader results
 - Critical adjunct findings communicated to El Camino on an individual basis
 - As the database builds, Personalis & El Camino assess the potential for a broader genome-scale joint diagnostic business

Proposed Working Relationship

- El Camino & Personalis work as a team
 - El Camino nominates a lead physician in each area of specialty
 - Personalis provides specialty-specific training on its genome interpretation
 - Team sets joint goals, periodically reviews metrics
 - El Camino provides Personalis with patient medical data as needed for regulatory filings
- El Camino has full medical & regulatory leadership & liability
- El Camino physicians & genetic counselors have full responsibility for the patient interface, medical records & consents

Regulatory Issues

- We work through physicians & genetic counselors, not direct to consumer
- Applied for CLIA approval of our laboratory and will seek CAP accreditation
- Our services are “high-complexity laboratory developed tests”
- Our interpretations will be physician consults, each signed by an MD
- Personalis has discussed its plans informally with FDA staff and been encouraged in our efforts to improve and document next-gen DNA sequencing accuracy
- Personalis is participating in a voluntary NIST consortium to develop US national standard reference materials for human genome sequencing. These may be used for NGS proficiency testing.
- Seeking a high-level clinical center to partner with:
 - Build success cases and document results for later regulatory base
 - Stanford hospital conflict-of-interest due to founders & investment



Genome Guided Medicine

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