Challenges and Opportunities in Translational Genomics

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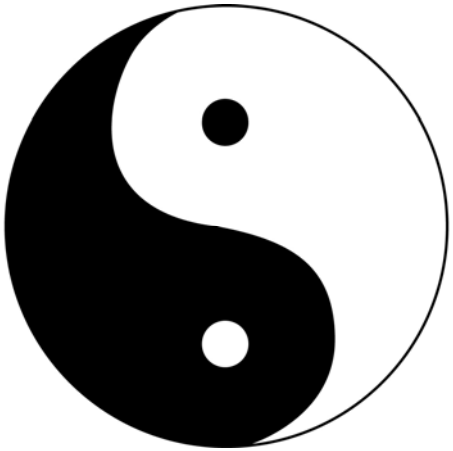
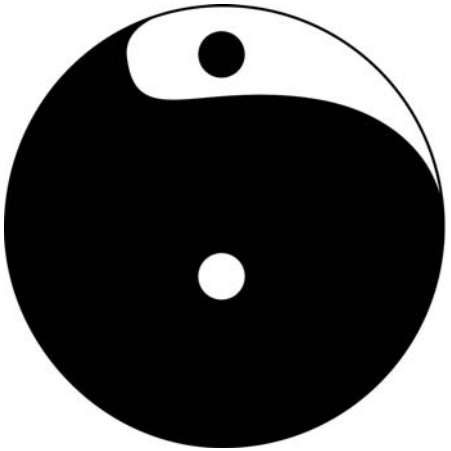
Genetic architecture of disease

Rare variants

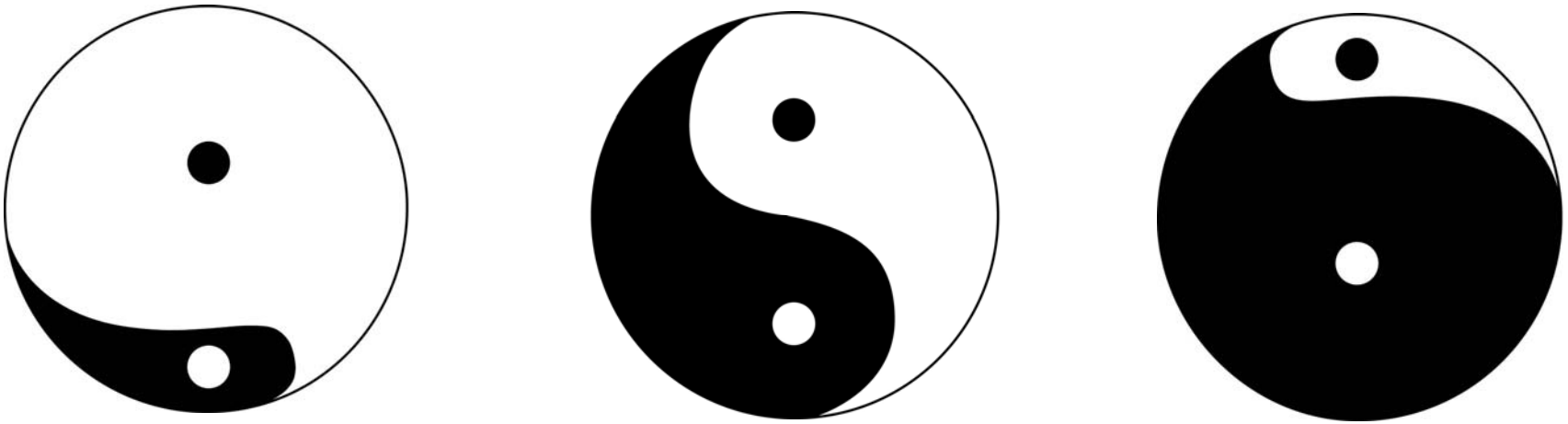




Common variants

Genetic architecture of disease

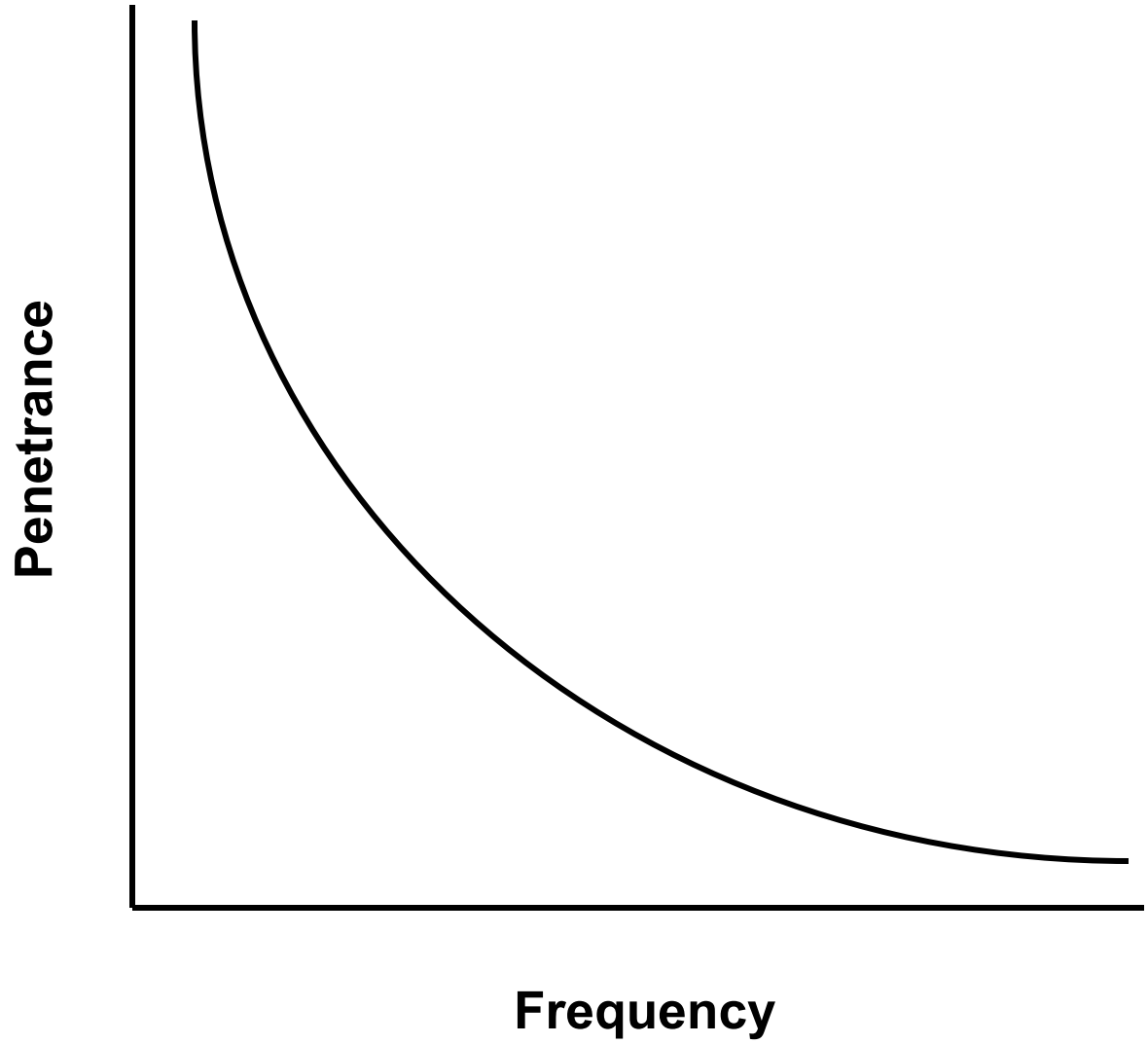
Rare variants



Common variants

We hypothesize that large-scale sequencing will allow a comprehensive assessment of the architecture of the genetic component of disease

Kinds of mutations



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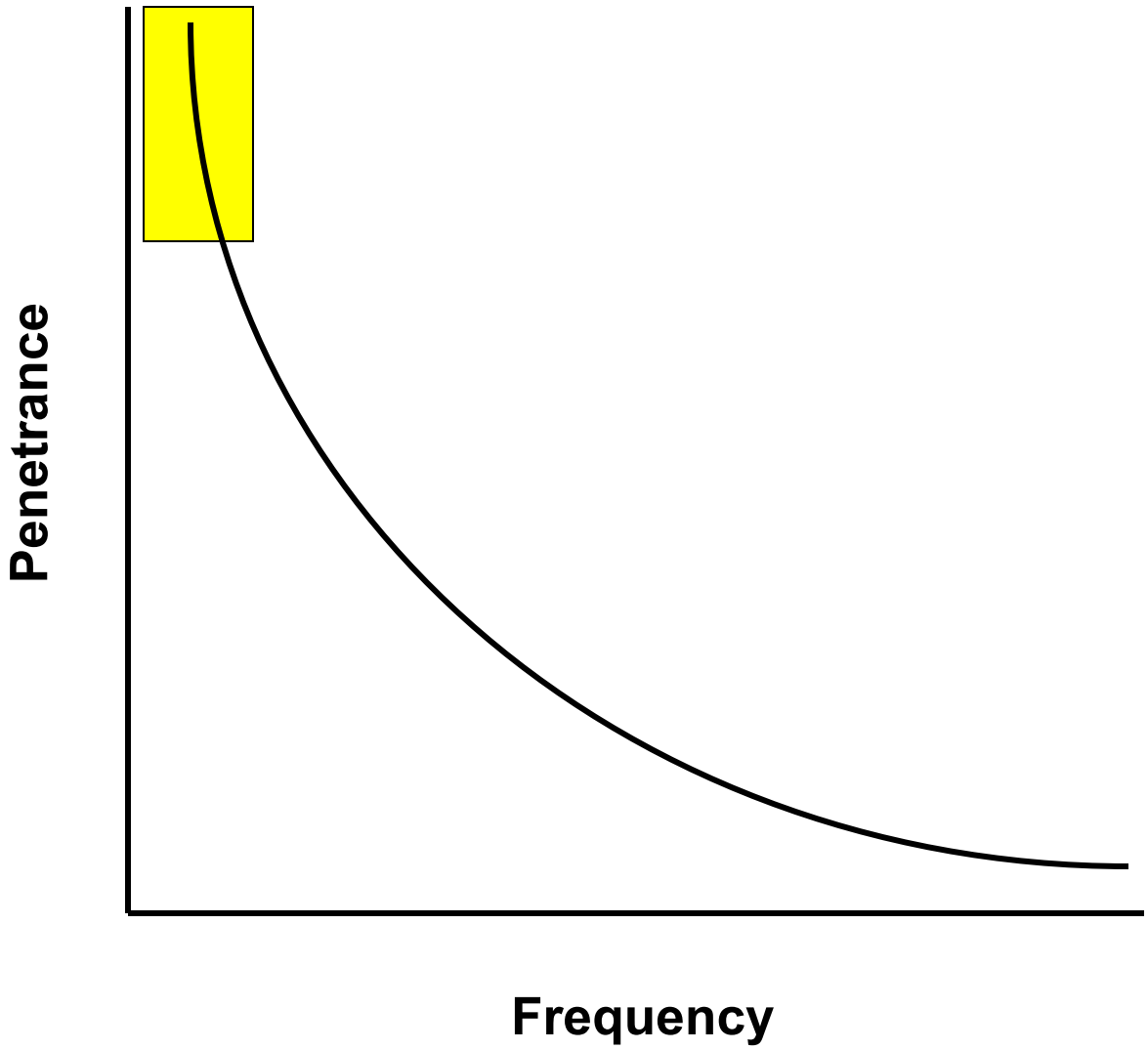

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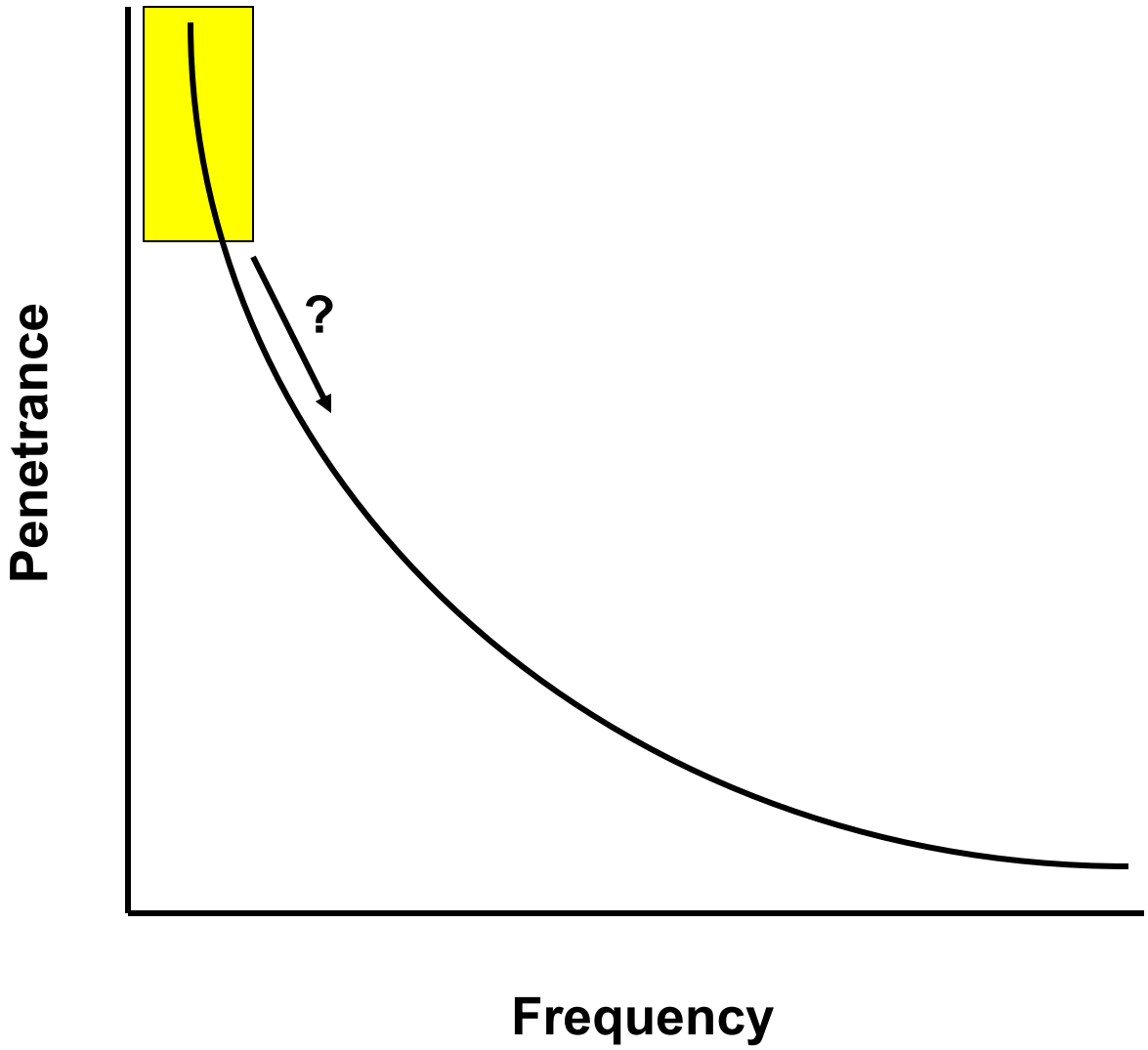


Translational genomics

- Genetic architecture of human disease
- Technologic advances
- New ways to ask and answer biomedical research questions

Translational genomics

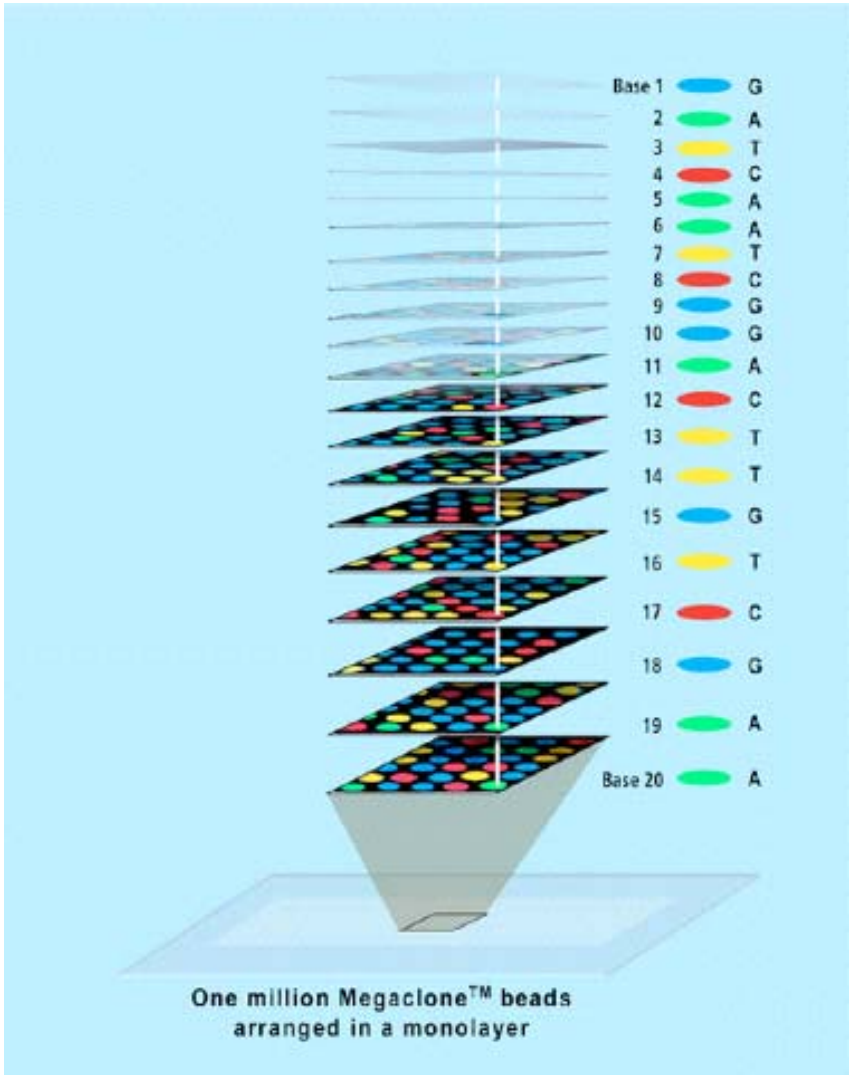
- **Genetic architecture of human disease**
- **Technologic advances**
- **New ways to ask and answer biomedical research questions**
  - ***Pilot whole genome sequence acquisition of individual subjects as a clinical research tool from consent to the return of results***

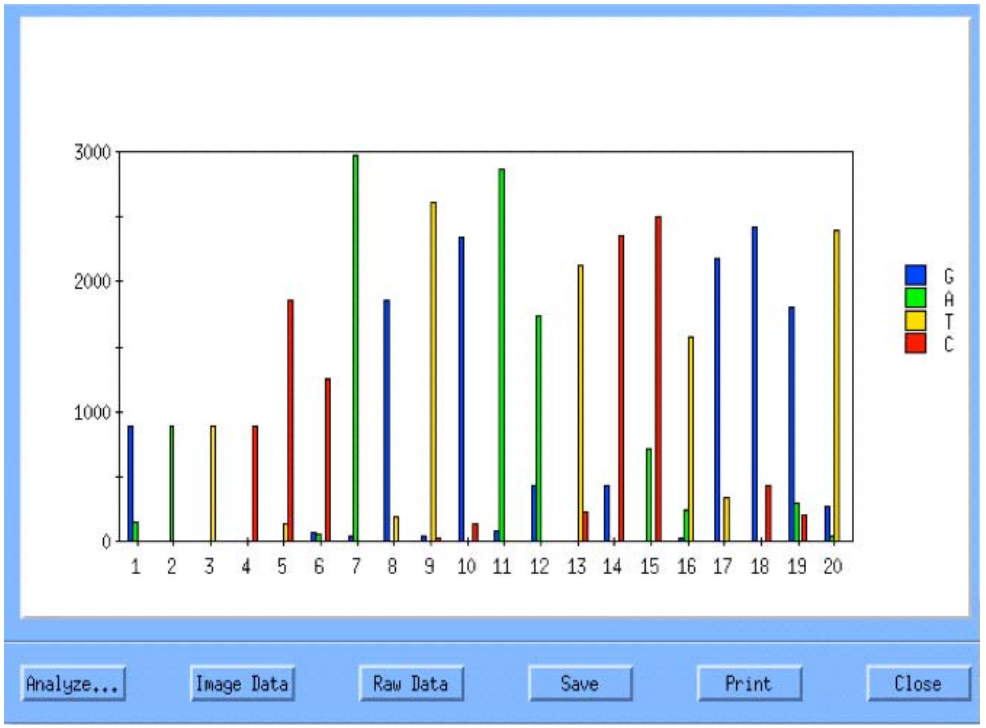
Sequencing technologies

NHGRI supported sequencing centers ~ 2 x 10^{11} bp/yr

Equivalent to 60 - 70 mammalian genomes/year

Solid phase sequencing





Up to 10^9 bp per run
$100,000 genome

ClinSeq: A translational research project in clinical genomics

Medical & Statistical Genetics

NHLBI

ClinSeq

NIH Clinical Center

NIH Intramural Sequencing Center

Specific aims

1. Develop a robust infrastructure for the generation and use of LSMS in a clinical research setting
2. Use LSMS data to develop novel approaches to clinical biomedical research
3. To understand how to interact with subjects re LSMS
4. Genetically dissect a phenotype with complex genetic architecture

Initial approach

- **Phenotype 1,000 subjects**
  - **Framingham risk score**
  - **250 patients into each of four bins**
    - **Low, medium, high risk, known disease**
- ***Initially* sequence 400 candidate genes**
  - **8,000,000 capillary reads**
- **Follow-up studies**
- **Interpret variants and validate *some***
- **Return results**

ClinSeq GeneList V6

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ABCA1	*CD40*	*HDAC2*	*MTP*	*ROS1*
ABCG1	*CD40LG*	*HMGCR*	*MVK*	*RXRA*
ABCG5	*CDKN1A*	*HMOX1*	*MYLK*	*SAR1B*
ABCG8	*CDKN2A*	*HMOX2*	*NCCT*	*SCARB1*
ACE	*CDKN2B*	*ICAM1*	*NFKB1*	*SCD*
ACTA2	*CELSR2*	*IL18*	*NKCC2*	*SELL*
ADH1C	*CETP*	*IL8*	*NOS1*	*SELP*
AGT	*CFH*	*INSIG2*	*NOS3*	*SELS*
AGTR1	*CIITA*	*ITGA2*	*NOX1*	*SERPINE1*
ADIPOR1	*CRP*	*ITGB1*	*NPC1*	*SIRT1*
ADIPOR2	*CXCR4*	*ITGB2*	*NPC1L1*	*SIRT3*
ADIPOQ	*CYBA*	*ITGB3*	*NPR1*	*SOAT1*
ALOX	*DGAT1*	*ITGB5*	*NRIH2*	*SOAT2*
ALOX5AP	*DGAT2*	*ITGB7*	*NRIH3*	*SOCS3*
ANGPTL3	*DUSP1*	*JAK3*	*NRF1*	*SOD2*
ANGPTL4	*ENPEP*	*KALRN*	*OLR1*	*SOD3*
ANRIL	*ESR1*	*KCNJ8*	*OR13G1*	*SORT1*
APOA1	*F13B*	*KCNMB1*	*P2RY12*	*SREBF1*
APOA2	*F2*	*KIF6*	*PAPPA*	*SREBF2*
APOA5	*F5*	*KL*	*PCSK9*	*STAT1*
APOB	*F7*	*LCAT*	*PDGFB*	*TAS2R50*
APOBEC1	*FABP2*	*LDLR*	*PDGFRB*	*TBXA2R*
APOC1	*FABP4*	*LDLRAP1*	*PER1*	*TCF1*
APOC2	*FAM5C*	*LGALS2*	*PITX2*	*TCF7L2*
APOC3	*FAS*	*LIPC*	*PLA2G4A*	*THBD*
APOC4	*FGB*	*LIPE*	*PLA2G7*	*THBS4*
APOE	*FGG*	*LIPG*	*PLAT*	*TIMP1*
APOM	*FLI1*	*LPA*	*PLTP*	*TLR4*
AR	*FOS*	*LPL*	*PON1*	*TLR8*
ARF	*FTO*	*LRP6*	*PPARA*	*TNFRSF1A*
ARG1	*GAL*	*LRP8*	*PPARD*	*TNFSF4*
ATF4	*GALNT2*	*LTA*	*PPARG*	*TRIB1*
BDKRB2	*GAS6*	*LTA4H*	*PRDX2*	*TRIB3*
BMI1	*GATA2*	*LTC4S*	*PRDX3*	*UCP2*
BSDL	*GCKR*	*MBL2*	*PRKG1*	*UCP3*
C11ORF2	*GCLC*	*MEF2A*	*PSMA6*	*USF1*
CALM1	*GCLM*	*MLXIPL*	*PSRC1*	*VAMP8*
CAPG	*GDF5*	*MMAB*	*PTGIS*	*VEGF*
CAV1	*GJA4*	*MMP3*	*PTGS1*	*VLDLR*
CCL2	*GP1BA*	*MMP9*	*PTGS2*	*VNN1*
CCR2	*GP1BB GP5*	*MOGAT1*	*RAP1B*	
CCR5	*GP6*	*MOGAT2*	*RBKS*	
CD36	*GPX1*	*MPO*	*ROMK*	

Progress

- Enrollment began January, 2007
- Nearly 350 patients enrolled mid May
- >900,000 sequence reads to date
- Results already returned

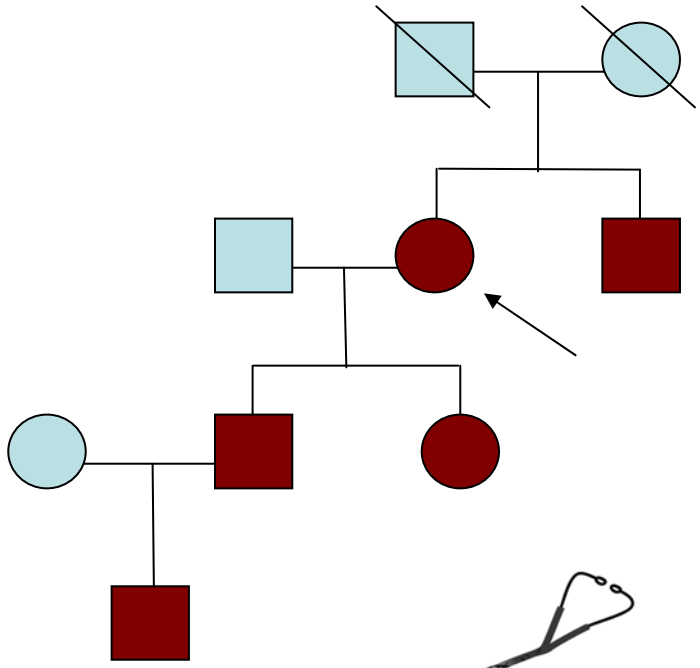
- **N=75 ClinSeq**
  - A50S
  - A391T
  - T726I
  - A391T
  - A391T
  - A391T
  - P685L
  - Y188X
  - A391T
  - V827I
  - A50S
  - T726I
  - R744Q:A391T
  - A391T
- **N=5 HapMap**
  - A391T

Initial ClinSeq LDLR variants

Medical history

- 65 yo female
- High cholesterol diagnosed at 25 years
- RX: atorvastatin, ezetimibe, hctz, lisinopril, niacin
- Coro Ca^{++} 1,726
- Chol 172, Trig 50, HDL 75, LDLd 88

- Family members diagnosed & treatment started



ClinSeq

What we will accomplish

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- Comprehensively dissect the genetic architecture of a phenotype
- Pilot approaches to personalized health care
- Ascertain the subject's views of LSMS

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- Develop molecular, bioinformatic & medical approaches for clinical LSMS
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- Ascertain the subject's views of LSMS
- Proceed to exome or genome sequencing - fully consented!

Public resource

- Clinical data deposited in dbGAP
- Sequences in trace archive
- Lymphoblast cell lines available
- Plasma/serum available (limited)

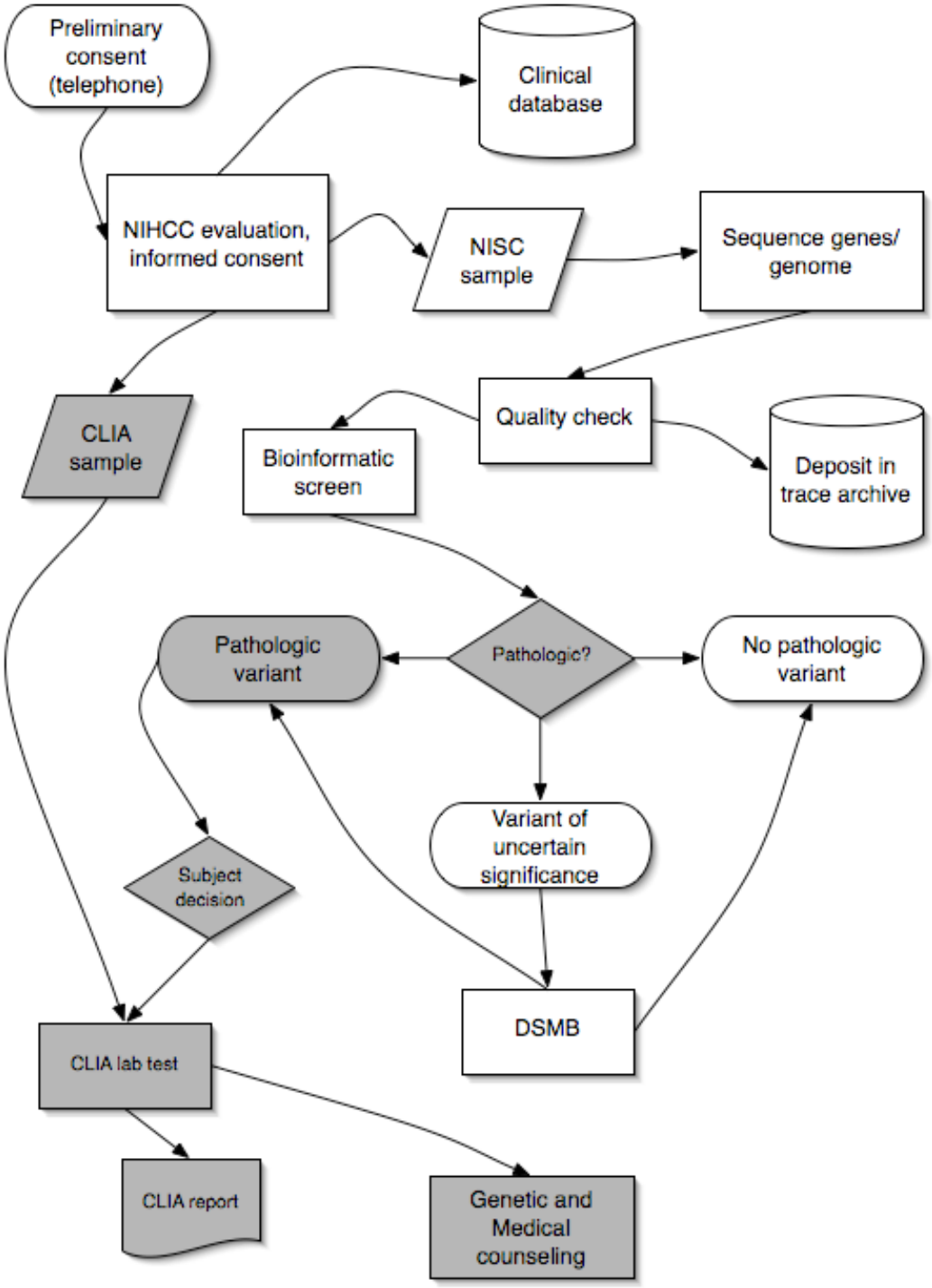
Hypothesis generating clinical research

- Collect patients with broadly defined clinical phenotype
- Sort on genomic attributes
- Refine phenotype of selected patients

Collaborators

- **NISC**
  - **Jim Mullikin, Bob Blakesly, Gerry Bouffard, Pedro Cruz, Nancy Hanson, Morgan Park, Alice Young**
- **NHGRI**
  - **Eric Green, Flavia Facio, Paul Gobourne, Jennifer Johnston, Teri Manolio, Jamie Teer, Clesson Turner, Alec Wilson**
- **NHLBI**
  - **Richard Cannon, Andrew Arai, Paul Hwang, Toren Finkel, Vandana Sachdev, Bob Shamburek**
- **NIHCC**
  - **Alan Remaley**

Results flow to subjects: Variants of clear clinical significance



Results flow to subjects: Variants of uncertain clinical significance