ClinSeq® Update
Secondary Findings & Predictive Medicine

Les Biesecker

NHGRI

Secondary Findings

- Intentional search for actionable mutations from exome/genome
  - Independent of indication for sequencing
- Distinct from incidental findings
  - Arbitrary, inadvertent discovery of variant
- Much derided, often avoided

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Secondary Findings

- Intentional search for actionable mutations from exome/genome
  - Independent of indication for sequencing
- Distinct from incidental findings
  - Arbitrary, inadvertent discovery of variant
- Much derided, often avoided
- But it is, in fact, predictive genomic medicine

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Genomic Precision Medicine

- What is it?
  - Predictive medicine, Personalized medicine, Individualized medicine, etc.
  - Stratify risks of disease, complications, prognosis
  - Maximize efficacy, minimize side effects
  - Must shift to genome-first approach, followed by iterative, *post hoc* phenotyping

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Combined Malonic & MethylMalonic Acidemia (CMAMMA)

- Autosomal recessive, childhood organic acidosis, decompensation, CNS infarcts, coma
- Exome identified *ACSF3* mutations
- ClinSeq® participant with homozygous variant
  - Post-hoc phenotyping – abnl metabolites
  - Late neurologic symptoms & abnl MRI
- Pre-hoc understanding of disease completely wrong

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Identification of novel phenotypes

- A mild form of type II diabetes mellitus in patients with mutations in *GCKR*, correlated with cellular localization


JCI The Journal of Clinical Investigation

Research article

Correlation of rare coding variants in the gene encoding human glucokinase regulatory protein with phenotypic, cellular, and kinetic outcomes

Matthew G. Rees,[1,2] David Ng,[1] Sarah Ruppert,[1] Clesson Turner,[1] Nicola L. Beer,[2] Amy J. Swift,[1] Mario A. Morken,[1] Jennifer E. Below,[3] Ilana Blech,[4] NISC Comparative Sequencing Program,[1] James C. Mullikin,[1] Mark I. McCarthy,[2,5,6] Leslie G. Biesecker,[1] Anna L. Gloyn,[2,6] and Francis S. Collins[1]

- *RGS6* null mutations lead to decreased heart rate variability


PLOS ONE

RESEARCH ARTICLE

Essential Role of the m_2R-RGS6-I_{KACh} Pathway in Controlling Intrinsic Heart Rate Variability

Ekaterina Posokhova, David Ng, Aaisha Opel, Ikuo Masuho, Andrew Tinker, Leslie G. Biesecker, Kevin Wickman, Kirill A. Martemyanov

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Secondary Findings are Predictive Genomic Medicine

- Broke this in 2006 with cancer susceptibility
- Followed with dysrhythmias, cardiomyopathy, & malignant hyperthermia

AJHG The American Journal of Human Genetics

ARTICLE

Secondary Variants in Individuals Undergoing Exome Sequencing: Screening of 572 Individuals Identifies High-Penetrance Mutations in Cancer-Susceptibility Genes

Jennifer J. Johnston,[1,7] Wendy S. Rubinstein,[1,2,3,7,8] Flavia M. Facio,[1] David Ng,[1] Larry N. Singh,[1] Jamie K. Teer,[1,4] James C. Mullikin,[1,4,5,6] and Leslie G. Biesecker[1,4,*]

Circulation: Cardiovascular Genetics

American Heart Association.

Original Article

Interpreting Secondary Cardiac Disease Variants in an Exome Cohort

David Ng, MD; Jennifer J. Johnston, PhD; Jamie K. Teer, PhD; Larry N. Singh, PhD; Lindsey C. Peller, BS; Jamila S. Wynter, BA; Katie L. Lewis, ScM; David N. Cooper, PhD; Peter D. Stenson, BSc; James C. Mullikin, PhD; Leslie G. Biesecker, MD; on behalf of the NIH Intramural Sequencing Center (NISC) Comparative Sequencing Program

ANESTHESIOLOGY

The Journal of the American Society of Anesthesiologists, Inc.

Using Exome Data to Identify Malignant Hyperthermia Susceptibility Mutations

Stephen G. Gonsalves, M.S.N.,* David Ng, M.D.,† Jennifer J. Johnston, Ph.D.,‡ Jamie K. Teer, Ph.D.,§ NISC Comparative Sequencing Program,‖ Peter D. Stenson, Ph.D.,# David N. Cooper, Ph.D.,** James C. Mullikin, Ph.D.,†† Leslie G. Biesecker, M.D.‡‡

ClinSeq™ TGCTGATCG

Secondary Variant Finding Validated by CSER Consortium

True Genomic Research Approach

- Search 950 exomes for all null variants
  - Nonsense, frameshift, splice
- Genes sensitive to haploinsufficiency
- Disease (not traits)
- Post-hoc phenotype

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- ~50% yield of disease
- 2-3% of participants
- Most undiagnosed
- Probably underestimate
  - Not all such genes known
  - Subset of mutations
  - Conservative phenotyping
  - Adults

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Lessons Learned

- Hypothesis-testing model limited
- Hypothesis-generating clinical research essential for predictive genomic medicine
- Unbiased ascertainment of phenotypes essential to knowing full spectrum
- Established concept of genomic secondary findings
- Established rate, 2-4%

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Lessons Learned

- Need to expand and scale hypothesis-generating clinical research
- Research requires
  - Thorough consent
  - Motivated cohort
  - Creative & motivated investigators

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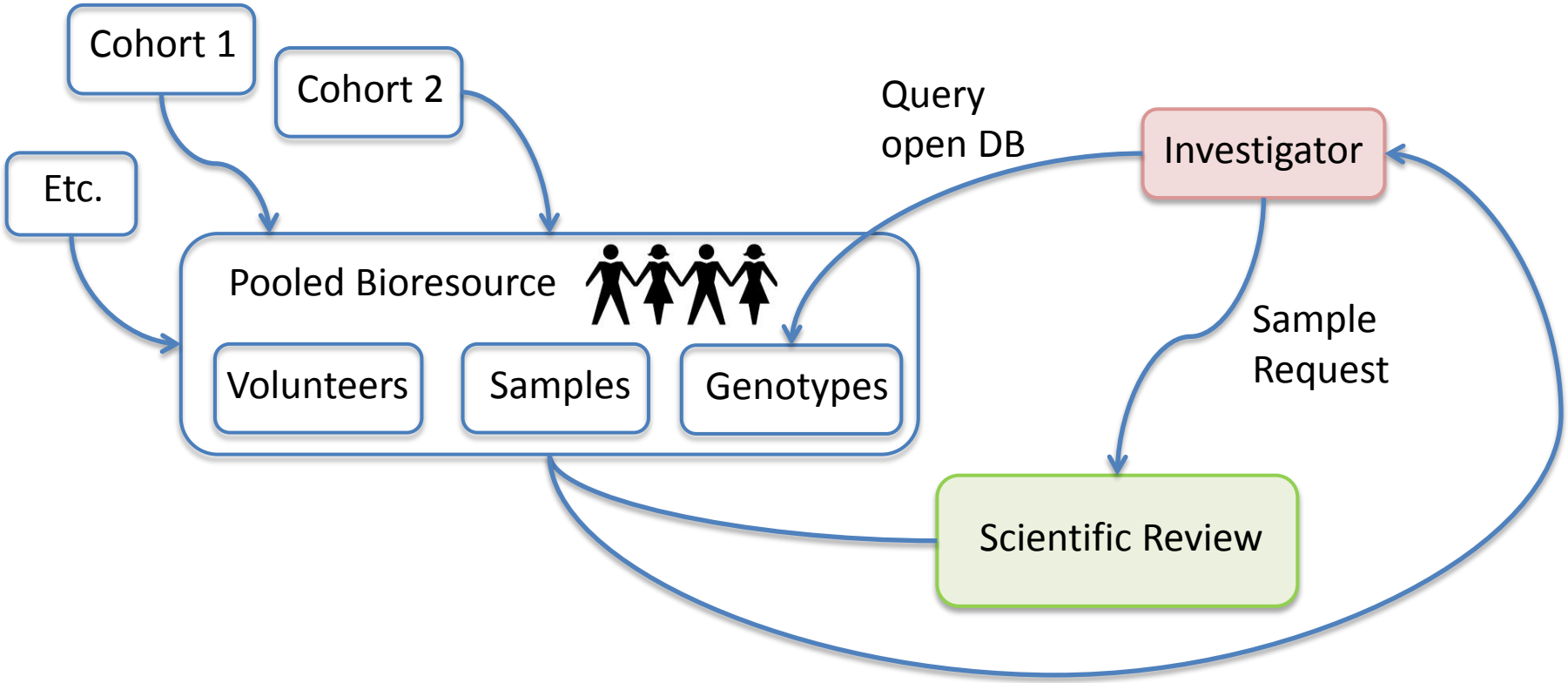
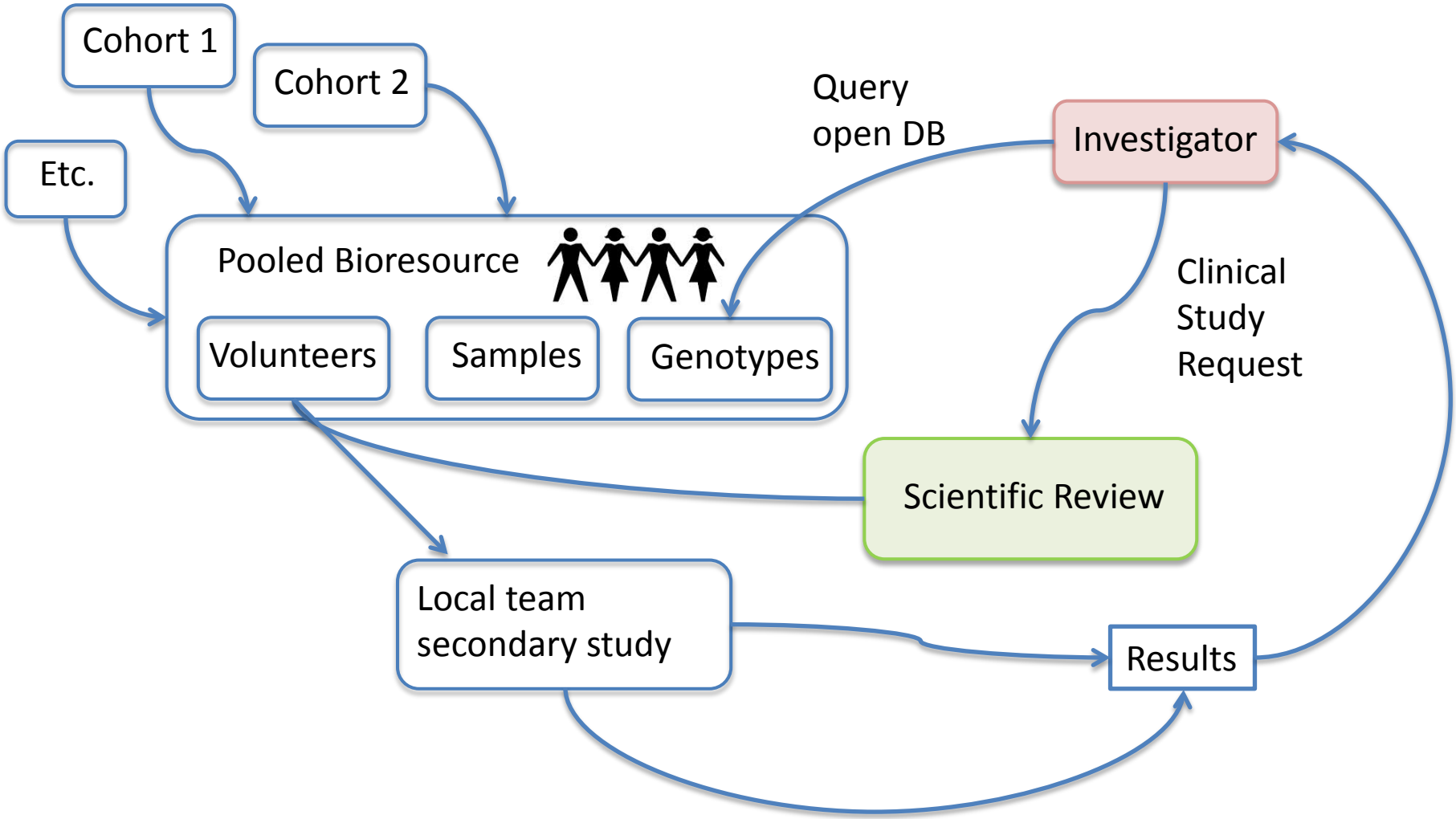
Iterative Research Project: Basic



Iterative Research Project: Clinical



Pushing Into Clinical Space

- Clinical Center Genomics Opportunity (CCGO)
- Two-track program
  - Exomes for researchers outside NHGRI
  - Exomes for clinical secondary findings analysis
- CLIA sequencing lab
- Objective to get clinical genomics to infiltrate into NIHCC practice

Conclusion

Think genomically in clinical research

Hypothesis generating research is valid, useful, and complementary to hypothesis-testing research