

# Genomics and Genetics Practice in Primary Care

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Annual Meeting  
Little Rock AR  
2016



# Definitions

## Personalized Medicine

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- The application of individual specific data to:
  - better target the delivery of health care
  - facilitate the discovery and clinical testing of new products
  - help determine a person's predisposition to a particular disease or condition
- Personalized medicine develops not only the tools to help providers deliver the care that works best “on average,” but at the same time develop a new class of tools for identifying and employing the best care for each individual patient.



# What's in a name?

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- “Personalized medicine: is understood by many as the use of individual sequence information to ensure the most appropriate selection of treatments
  - Often distilled as “the right drug at the right dose for the right person
- My choice
  - Genomically-directed medicine (GDM)

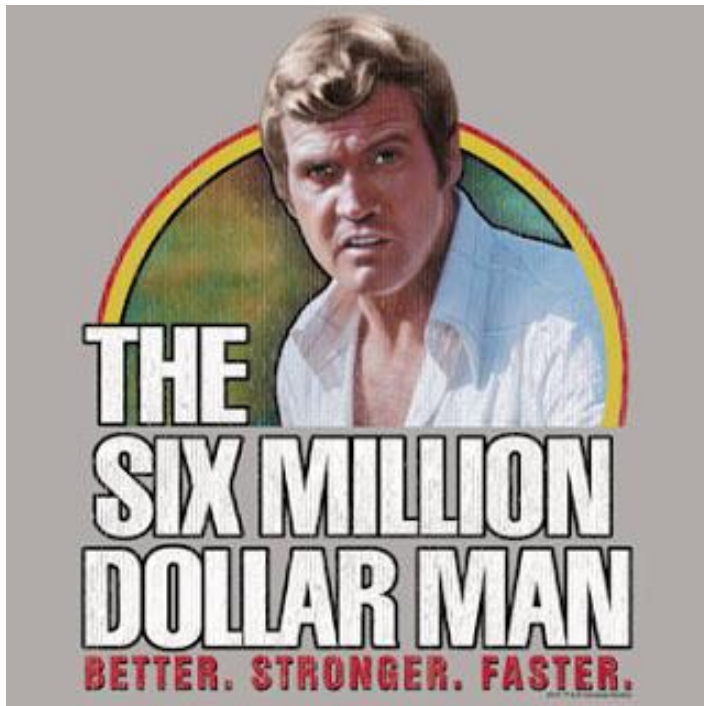


# Genomically Directed Medicine

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- Using personal and familial genomic information to individualize:
  - Diagnostics
  - Prognostics
  - Therapeutic plans
  - Prevention strategies
  - Heritability predictions

# We have the technology



- Following in the tradition of President Kennedy's call to action of sending a man to the moon and returning him safely to earth, in January 2015, at a State of the Union address, **President Obama announced the call to action of the Precision Medicine Initiative.** This Initiative has the ultimate goal of moving the United States into the era where medical treatment will be tailored to each patient.

# APPLICATIONS IN CLINICAL MEDICINE



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# 1. FAMILY HISTORY

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- A 3 generational pedigree should be obtained and periodically updated on all families in your practice
- This includes the patient, their siblings, parents, aunts, uncles, cousins, and grandparents
- If the patient is an adult it may also include the patients children and grandchildren
- Further generations should be included if the patient knows relevant health history for those more distant relatives

# The Family History in Personalized Medicine

"Why waste your money looking up your **family tree**? Just go into politics and your opponents will do it for you."  
-Mark Twain

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- It has been consistently shown that obtaining and correctly interpreting a pedigree can identify an etiologic diagnosis as often as any genomic test



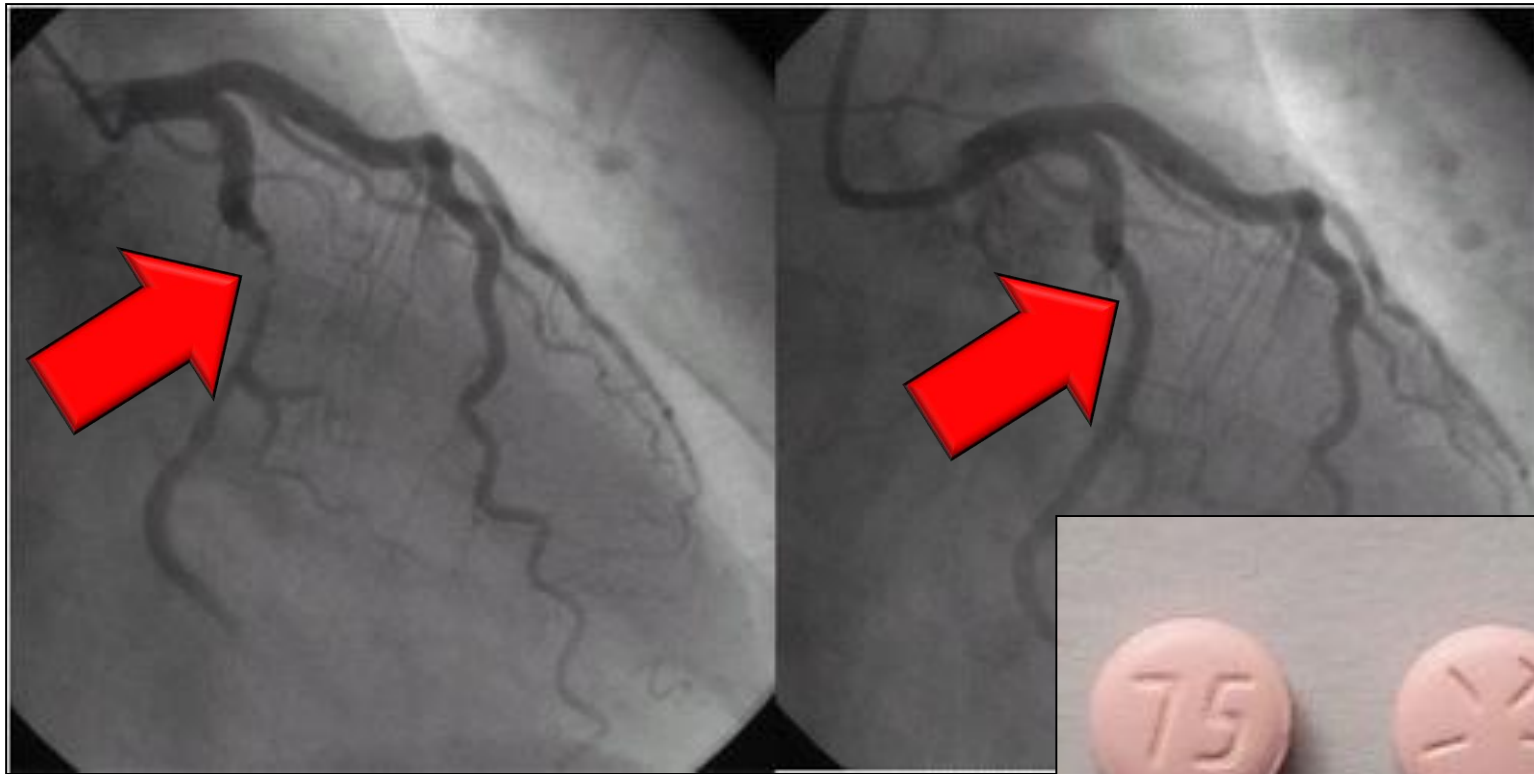


## 2. Pharmacogenomics

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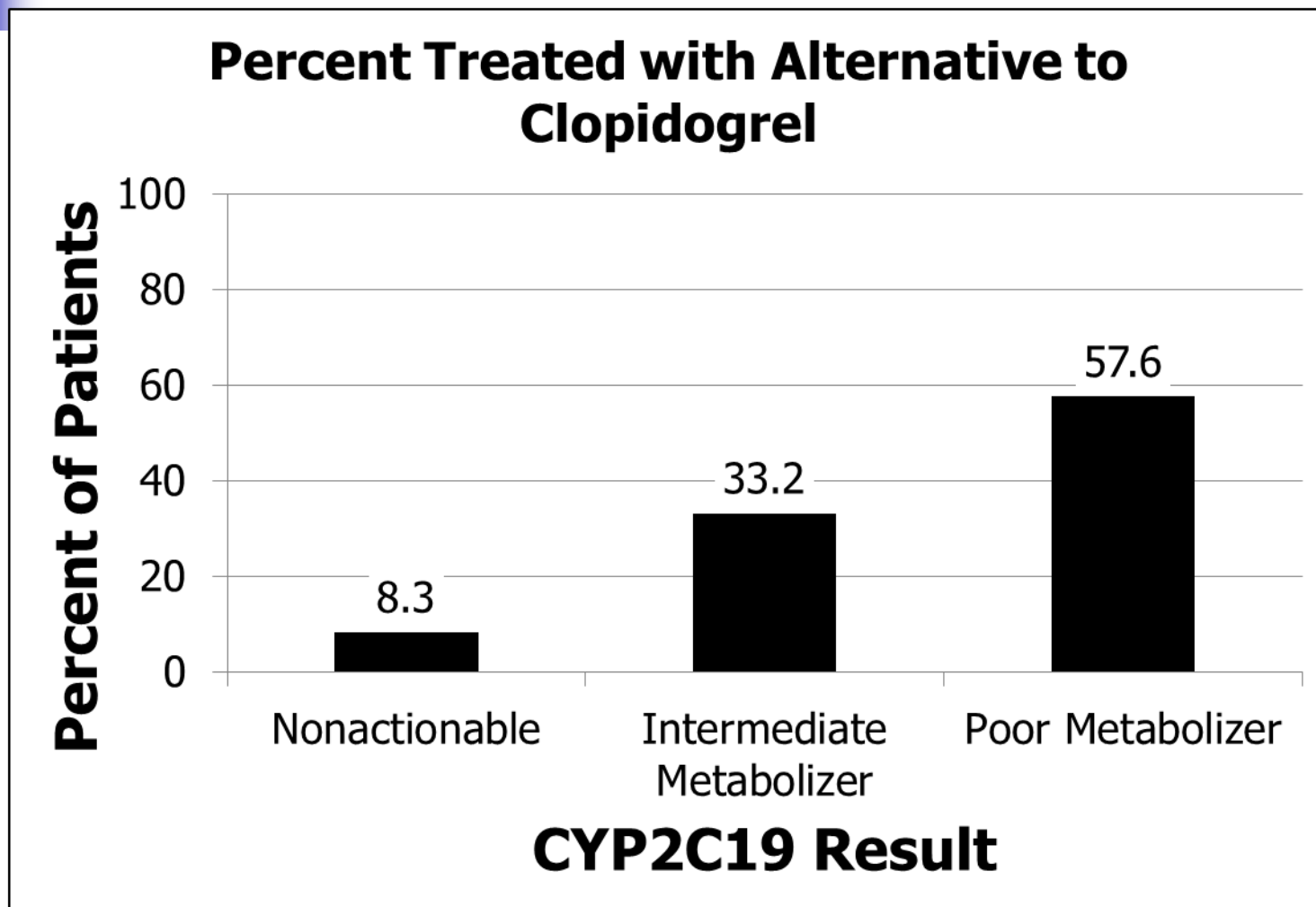
# Clopidogrel

Secondary Prevention in  
Heart Attack: A Precision Medicine Success Story



# What is the impact of genotyping?

*real clinical*






SEARCH

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## Drugs

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### Science & Research (Drugs)

#### Additional Research Areas

#### Genomics

[Overview of the Genomics and Targeted Therapy Group](#)

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### Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Biomarkers in the table include are not limited to germline or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities.

This table does not include non-human genetic biomarkers (e.g., viral or bacterial) i.e., microbial variants that influence sensitivity to anti-infectives; biomarkers that are used solely for diagnostic purposes unless they are linked to drug activity or used to identify a specific subset in whom prescribing information differs (e.g., for genetic diseases). Therapeutic areas do not necessarily reflect the FDA review division.

Pharmacogenomic information can appear in different sections of the labeling. Relevant sections of the labeling with such information are noted in the last column of the table. For more information on the relevance of information in various parts of drug labeling (e.g. Indications and Usage, Dosage and Administration, Boxed Warning, etc.), please refer to the appropriate [labeling guidance](#). For information on the FDA's initiative to improve prescription drug labeling, visit the [FDA/CDER Learn website](#).

## Pharmacogenomic Biomarkers in Drug Labeling

Drug	Therapeutic Area	HUGO Symbol	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	EGFR exon 19 deletion or exon 21 substitution (L858R) mutation positive	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Amitriptyline	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions
Anastrozole	Oncology	ESR1, PGR	Hormone receptor positive	Indications and Usage, Clinical

> 160  
10/10/2016



# 3. Prevention

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# Baylor Adult Disease Prevention Study

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- Used volunteers from the Young Presidents Organization
- 81 volunteers
  - Medical history positive in 25 for disease gene association
  - Family history positive in 4
  - SNP analysis
    - 270 AR
    - 10 XLR
    - 170 AD



# Baylor Adult Disease Prevention Study

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- Examples of positives:
  - NSHL
  - ASHD
  - BRCA
  - Type II DM
  - Obesity (MC4R)
  - Xanthanuria (not clinically sigif)
  - Thyroid
  - Melanoma
  - Prostate Ca
  - Macular degeneration
  - RP





# 4. Translation into Clinics

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# UAMS Personalized Medicine Clinics

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- Initiative by Dean Richard Smith
- 2 Phase projects
  - RFP
  - Phase 1 planning
  - Phase 2 Implementation



# UAMS Translational GDM Clinics

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- Colorectal cancer
- Ocular genetics
- Type III diabetes
- Hyperlipidemia
- Precision Psychiatry
- Wellness (FP)
- Pediatrics (approved, not funded)



# NSIGHT

(Newborn Sequencing in Genomic Medicine and Public Health)

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- 4 projects funded by NICHHD
  - 26 hour genomes for the management of critically ill newborns
  - Genomes in healthy newborns
    - Newborn exome sequencing for universal screening (2)
    - Not tied to NBS (1)

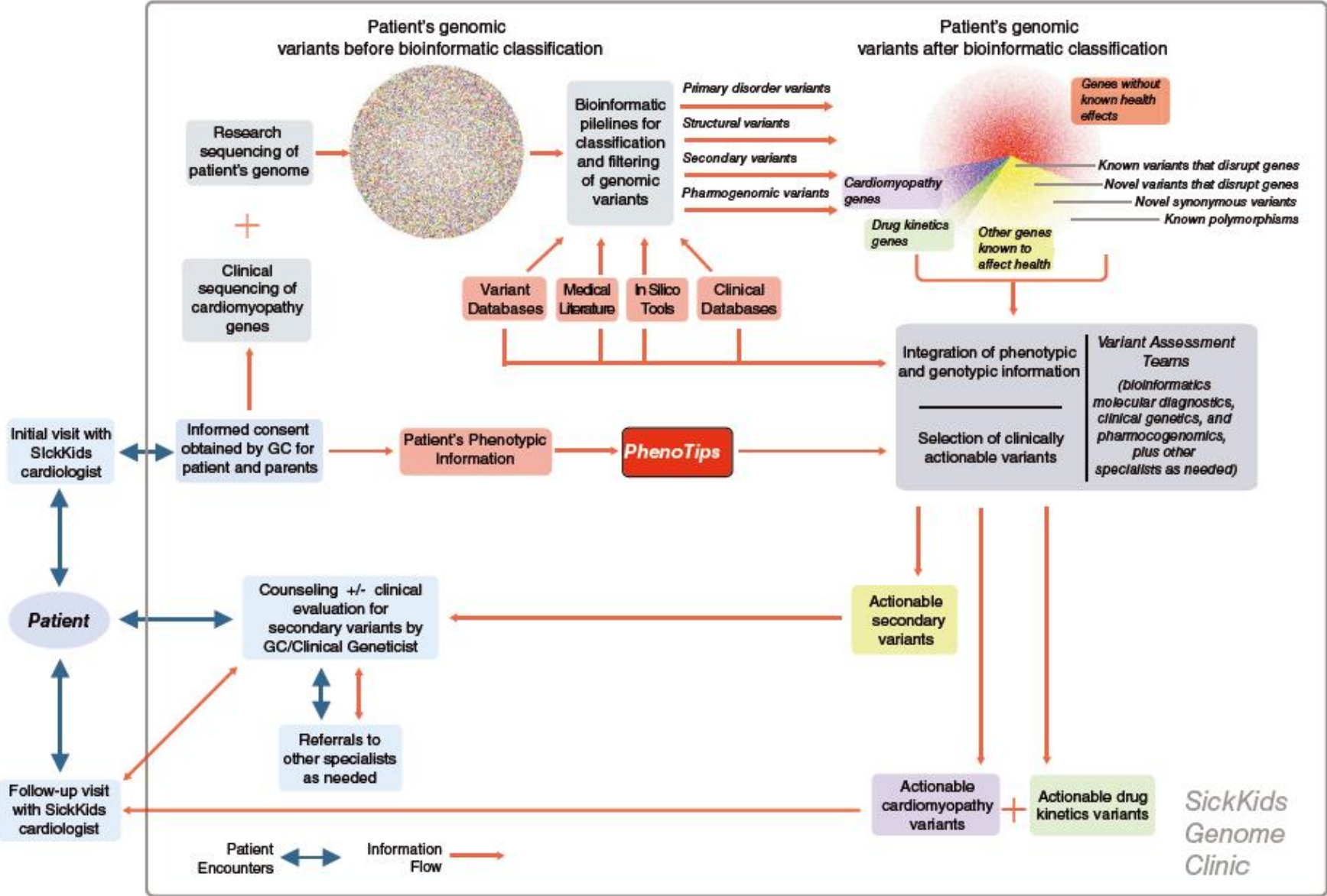
DIAGNOSTICS

# Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,<sup>1,2,3,4,5\*</sup> Neil Andrew Miller,<sup>1,2,4\*</sup> Sarah Elizabeth Soden,<sup>1,2,4\*</sup> Darrell Lee Dinwiddie,<sup>1,2,3,4,5\*</sup> Aaron Noll,<sup>1</sup> Noor Abu Alnadi,<sup>4</sup> Nevene Andraws,<sup>3</sup> Melanie LeAnn Patterson,<sup>1,3</sup> Lisa Ann Krivohlavek,<sup>1,3</sup> Joel Fellis,<sup>6</sup> Sean Humphray,<sup>6</sup> Peter Saffrey,<sup>6</sup> Zoya Kingsbury,<sup>6</sup> Jacqueline Claire Weir,<sup>6</sup> Jason Betley,<sup>6</sup> Russell James Grocock,<sup>6</sup> Elliott Harrison Margulies,<sup>6</sup> Emily Gwendolyn Farrow,<sup>1</sup> Michael Artman,<sup>2,4</sup> Nicole Pauline Safina,<sup>1,4</sup> Joshua Erin Petrikin,<sup>2,3</sup> Kevin Peter Hall,<sup>6</sup> Stephen Francis Kingsmore<sup>1,2,3,4,5†</sup>

Monogenic diseases are frequent causes of neonatal morbidity and mortality, and disease presentations are often undifferentiated at birth. More than 3500 monogenic diseases have been characterized, but clinical testing is available for only some of them and many feature clinical and genetic heterogeneity. Hence, an immense unmet need exists for improved molecular diagnosis in infants. Because disease progression is extremely rapid, albeit heterogeneous, in newborns, molecular diagnoses must occur quickly to be relevant for clinical decision-making. We describe 50-hour differential diagnosis of genetic disorders by whole-genome sequencing (WGS) that features automated bioinformatic analysis and is intended to be a prototype for use in neonatal intensive care units. Retrospective 50-hour WGS identified known molecular diagnoses in two children. Prospective WGS disclosed potential molecular diagnosis of a severe *GJB2*-related skin disease in one neonate; *BRAT1*-related lethal neonatal rigidity and multifocal seizure syndrome in another infant; identified *BCL9L* as a novel, recessive visceral heterotaxy gene (*HTX6*) in a pedigree; and ruled out known candidate genes in one infant. Sequencing of parents or affected siblings expedited the identification of disease genes in prospective cases. Thus, rapid WGS can potentially broaden and foreshorten differential diagnosis, resulting in fewer empirical treatments and faster progression to genetic and prognostic counseling.

# The SickKids Genome Clinic





# ACH Genomic Medicine Initiative

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Together, ACHRI and the UAMS COM Department of Pediatrics are pleased to announce our intention to establish an innovative, cutting-edge new program in genomic and precision medicine. The program, which is being developed under the capable direction of Drs. Brad Schaefer and Laura James, will marry our strong academic programs in Genetics and Pediatric Clinical Pharmacology. Together, Brad and Laura will assemble a cross-disciplinary task force to design the program and develop the requisite business plan. This program will be one of few of its kind in the US operating within a free-standing academic children's medical center. We look forward to sharing with you additional details about the program in the coming months.

- Gregory L. Kearns, PharmD, PhD, FCP, FAAP



# Arkansas Children's Personalized Medicine Clinic for Neurodevelopmental and Neurobehavioral Disorders

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- Quaternary referral clinic
- Multidisciplinary
  - Genetics / genetic counseling
  - Clinical pharmacology
  - Developmental pediatrics
  - Child psychiatry
  - Child psychology
  - Developmental pediatrics
- Customized genomic analysis for relevant genes in:
  - Diagnosis
  - Predicted response to therapy
  - Pharmacogenetics
  - Drug metabolism (PK/PD)
  - Adverse / side effects (incl suicide risk)