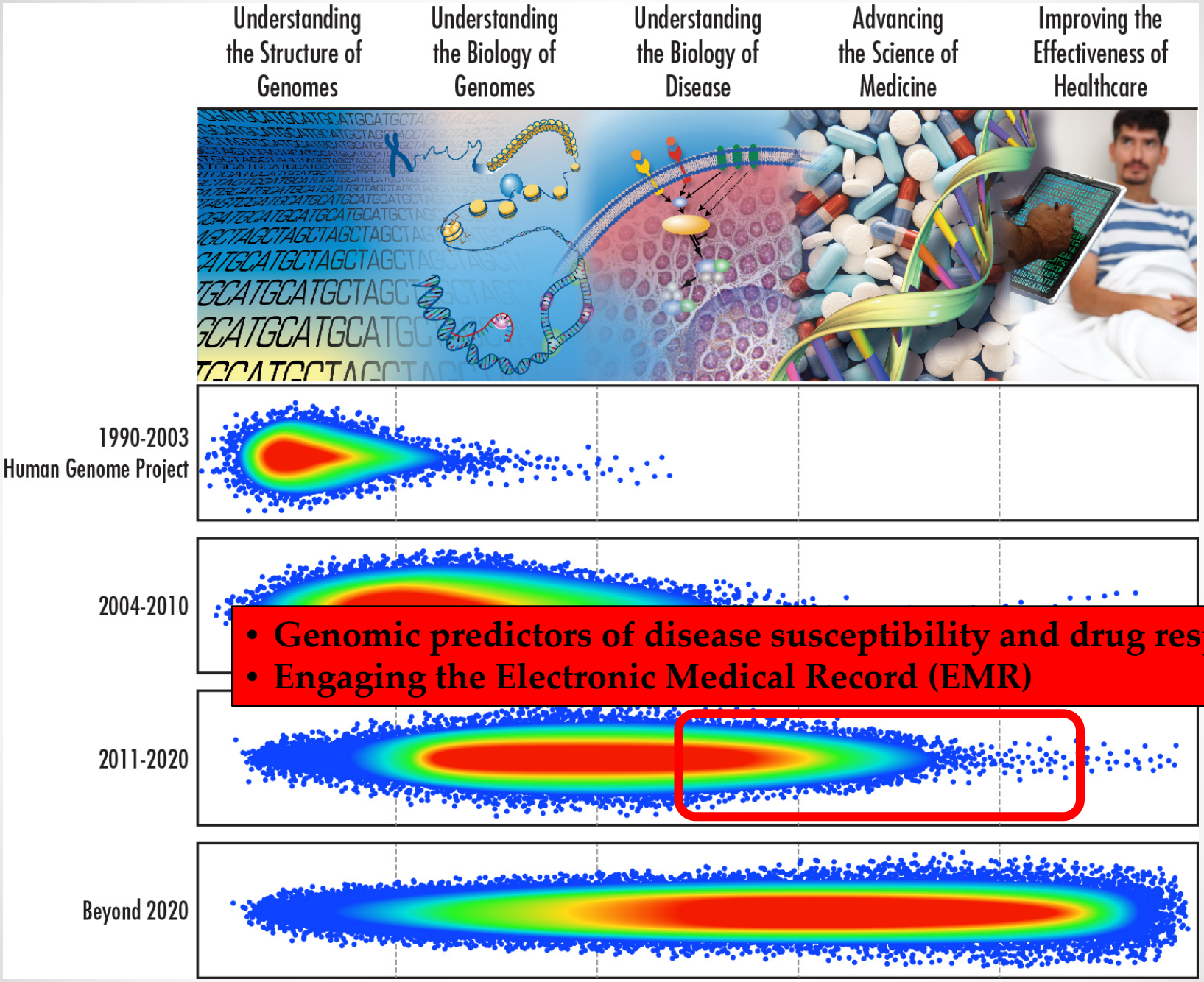
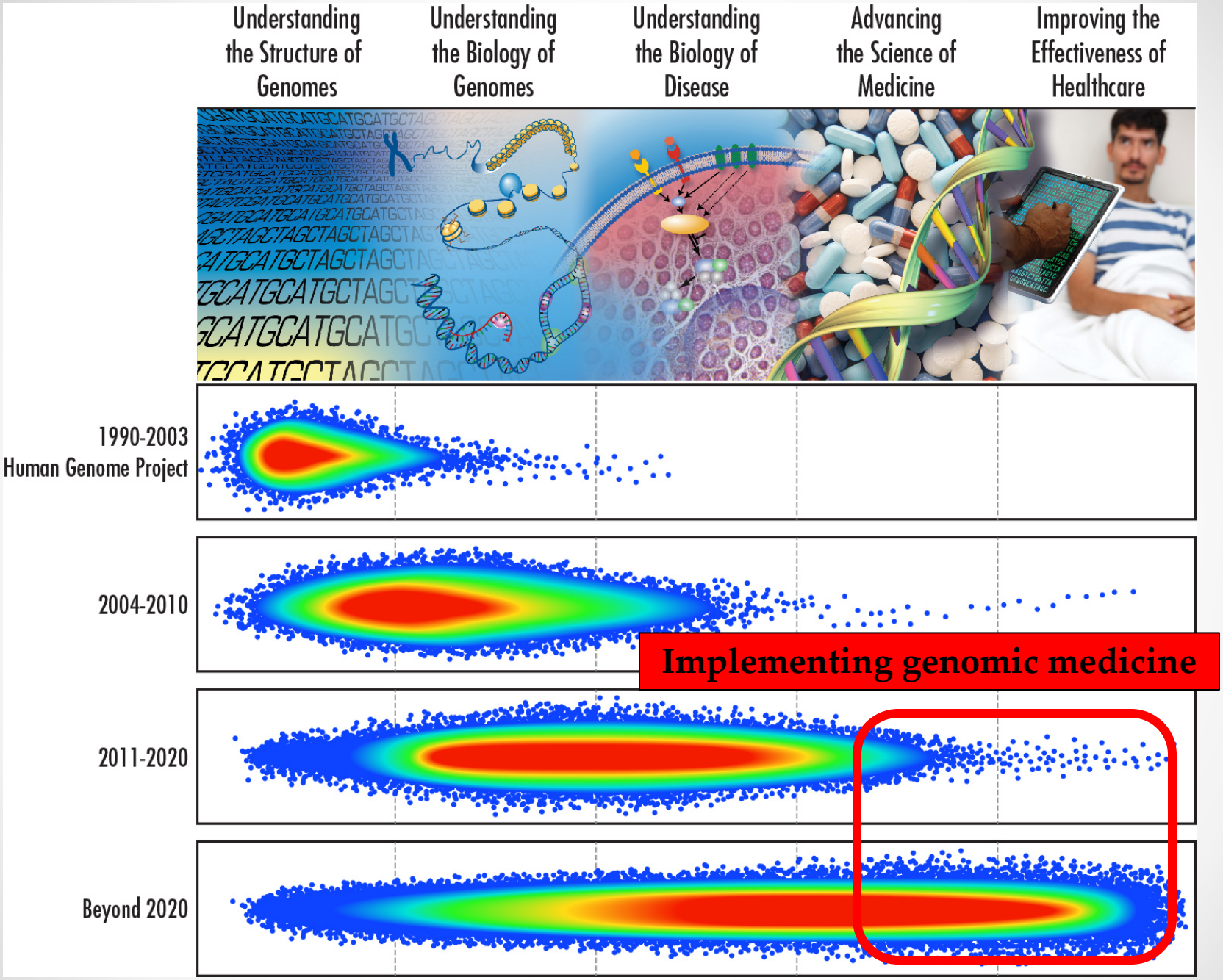
Future Opportunities for Genome Sequencing

Genome Sequencing for Clinical Care

Dan M. Roden, MD



Green and Guyer,. 2011



Green and Guyer,. 2011

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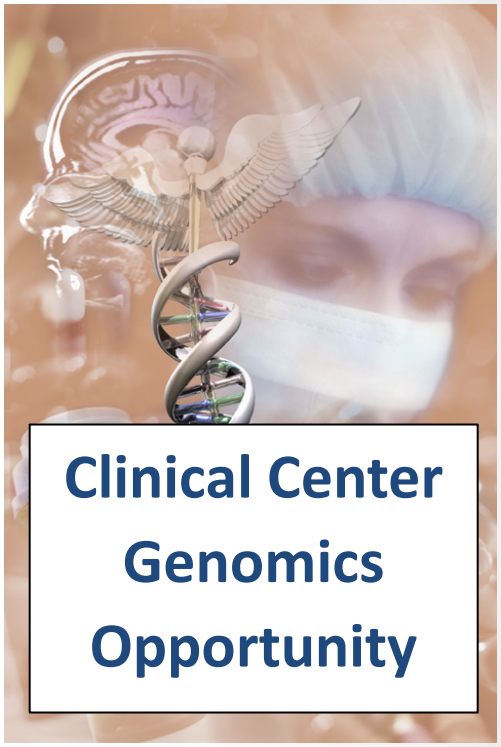
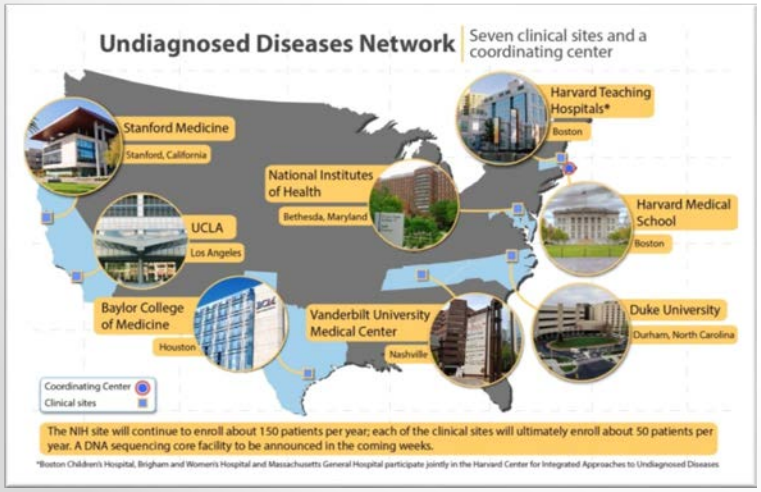
Clinical Sequencing Exploratory Research

IGNITE Implementing GeNomics In pracTicE

Global Leaders in Genomic Medicine 2014



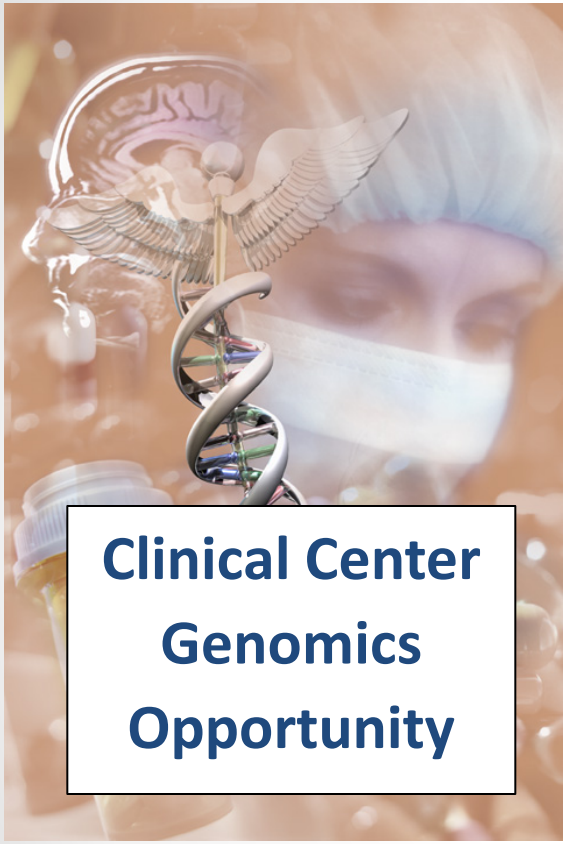


eMERGE Network

electronic medical records & genomics

Demonstration projects to incorporate genomic information into EMRs with decision support

- family history
- hypertension management in AAs
- Pharmacogenetic variant implementation
- Diabetes diagnosis: Sequencing ~40 diabetes/ lipodystrophy/obesity genes in targeted patients



- ~1000 exomes: projects 50-300 exomes each
- Evidence for Mendelian, single gene etiology
  - Actual NIHCC patients
  - Germline prioritized over somatic sequencing
- Consent & protocol language in place
- Sequencing at NIH intramural center; “CLIA valid”
- PI designates staff for analysis of primary variants; returns primary findings
- NHGRI analyzes & returns secondary findings

eMERGE Network

electronic medical records & genomics

- >350,000 subjects with DNA samples + EMRs across 10 sites
- electronic phenotyping; GWAS genotyping
  - phenotype → genotype
  - genotype → phenotype ("PheWAS")
- eMERGE-PGx: Targeted sequencing across pharmacogenes

GroupHealth · Marshfield Clinic · University of Washington · Essentia Health (Here with you) · Mount Sinai School of Medicine · Geisinger · The Children's Hospital of Philadelphia · Mayo Clinic · Boston Children's Hospital · Northwestern University · Cincinnati Children's Hospital Medical Center · Vanderbilt University

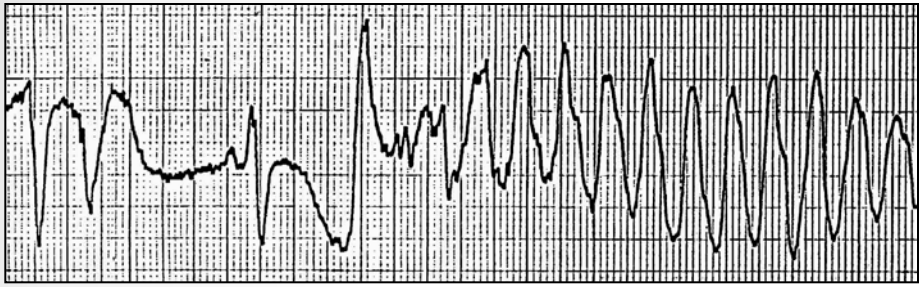
eMERGE-PGx Pharmacogene sequencing project

- identify patients
- identify “actionable” variants
- sequence

implement actionable variants

create a repository of all variants

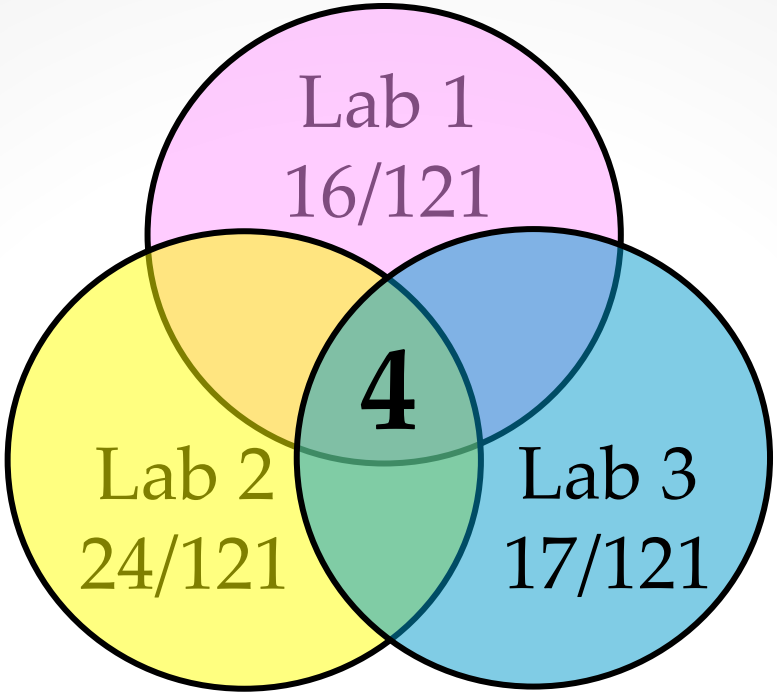
A variant of unknown significance problem



congenital long QT syndromes caused by mutations in ion channel genes, including *SCN5A* and *KCNH2*

Of the first 2,022 eMERGE-PGx subjects

- 128 non-synonymous variants in *SCN5A* and *KCNH2*
- 121/127 MAF <0.5%; 92 singletons
- 3 expert annotators asked to assign pathogenicity



EMR review (n=48):

- 1 with atrial fibrillation
- 31/48 with ECGs: 1/31 with long QT

Issues:

- return which results? which (if any) patients to have ECGs? screen families? which? what if new data changes the interpretation?

ClinGen

The Clinical Genome Resource

Launched Sept 2013

NCBI ClinVar Leads	U41 Grant PIs	U01 PIs	U01 PIs	NHGRI/NICHD/NCI Program Directors
Melissa Landrum Donna Maglott Steve Sherry	David Ledbetter Christa Martin Bob Nussbaum Heidi Rehm	Jonathan Berg Jim Evans David Ledbetter Mike Watson	Carlos Bustamante Sharon Plon	Erin Ramos Lisa Brooks Danuta Krotoski Sheri Schully

- ClinVar is a database developed and maintained by NCBI with input from the community, including ClinGen investigators
- ClinGen, The Clinical Genome Resource:
  - Standardizing, sharing, and developing new methods for annotation, interpretation, and assessment of actionability of genomic variants

- 3,500 patients, 10 projects
- Individualized phenotypes → genotype
- Standardized exome/genome sequencing and reporting
- Ongoing ELSI assessments

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- Healthy individuals
- Preconception carrier screening
- Cardiomyopathy
- Childhood cancers
- Adult cancers
- Susceptibility to colon cancer and polyps
- Intellectual disabilities
- Hearing loss

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Major questions

- Patient characteristics that signal potential utility of whole genome or exome sequencing
- How to analyze large data sets in a clinical environment
- Special considerations in different populations
- Management of “non-target” data

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The numbers

As of March 2014:

- 1,532 subjects; 69% adult; 52% female
  - White 74%
  - African American 7%
  - Hispanic 8%
  - Asian 3%
  - American Indian 2%
  - Not Reported 7%
- Total Sequenced: 1049
  - 232 Tumor-focused
  - 817 Germline-focused

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The numbers

Germline analysis (n=817)

- "Positive" for diagnostic finding: 241 (29%)
- Incidental Findings per ACMG list: 24 (2.9%)
  - Incidental Findings by relaxed criteria: 46 (5.6%)

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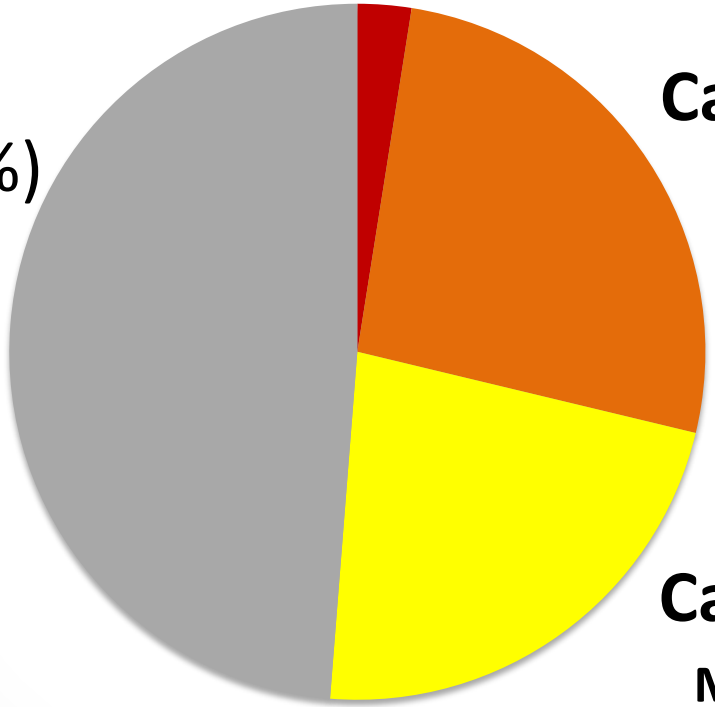
Diagnostic yield by initial diagnosis (Germline analyses)

	Cases	*(+)*	*Possible*	*(-)*	*Yield*
Cancer (Pediatric)	115	11	10	94	18%
Cancer (Adult)	109	9	25	75	31%
Dysmorphology	41	10	7	24	41%
Heart Disease	48	10	11	27	44%
Bilateral sensorineural hearing loss	24	3	8	13	46%
Neurological Diagnosis	108	24	27	57	47%
Retinal	41	8	13	20	51%
Preconception (Carrier)	7	5	0	2	71%

Pediatric Solid Tumor exome results

Highest category somatic mutation found per patient (n=81)

Category 1 (2%)
Mutations of "established clinical utility" in that tumor type



Category 2 (26%)
Mutations of "potential clinical utility"

Category 4 (49%)
Only somatic mutations in "non-cancer genes"

Category 3 (23%)
Mutations in other known "cancer genes"

BASIC^3
BCM Advancing Sequencing Into Childhood Cancer Care

Baylor College of Medicine

Texas Children's Cancer Center

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A major focus on ELSI from the onset

- Informed consent :
  - analysis across sites
  - formulation of specific recommendations for best practices
  - Factors influencing patient understanding & outcomes
- Incidental Findings
  - Frequency of “medically actionable” incidental findings: 3-6%
  - CSER sites input into ongoing ACMG policy formulation on return of results
  - Accruing data on what patients wish to know
- Collecting data on measures of patient satisfaction/distress with regard to both diagnostic findings and off-target results

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Going forward

Assessing the impact of sequencing findings across time and families:

- Of the patients with incidental findings, how many had clinical work-ups for the condition
- Of these patients how often were there phenotypic features of the genotype described.
- Derive initial cost-effectiveness assessments of the reporting of incidental findings.
- How are findings transmitted to family members
- Issues of re-interpretation of genomic data after the initial report

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IGNITE Implementing GeNomics In practicE

eMERGE Network
electronic medical records & genomics

Undiagnosed disease network

Common issues

- EMR integration
- Return of results
- Actionability: target and incidental
- Data sharing concerns
- Longitudinal issues: what happens to patients over time? What happens when interpretation changes over time?

Global Leaders in Genomic Medicine 2014

Genomic Medicine working group: meeting 6

Opportunities for international collaborations

50 participants
25 countries

Genomic Medicine working group: meeting 6

Opportunities for international collaborations

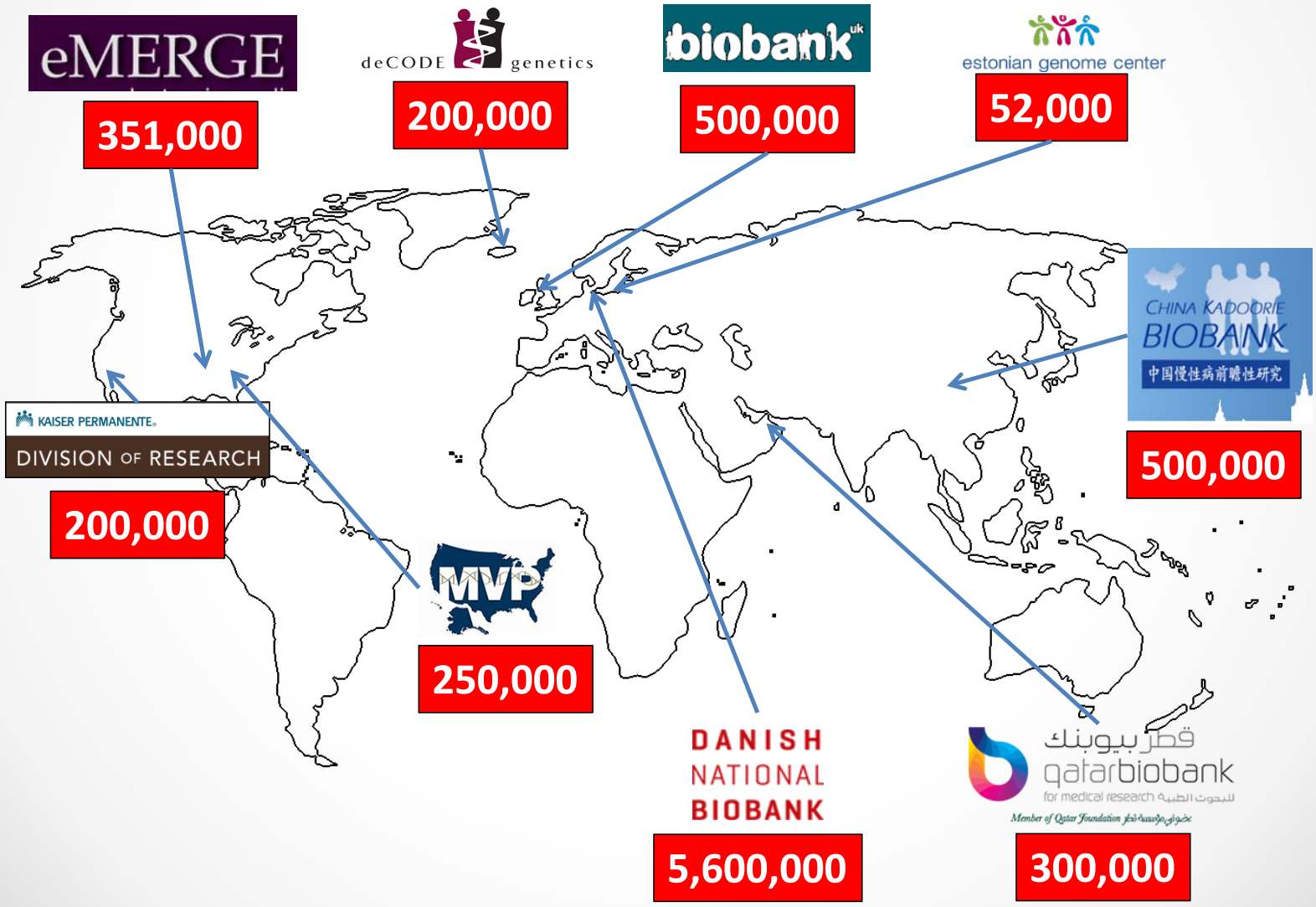
- Evidence generation
- Health information technology
- Education/workforce development: Genomics professionals; bioinformatics expertise ; Other health professionals; Public
- Pharmacogenomics
- Policy: Data sharing and regulatory issues; Costs and benefits

GM6: Clinical capabilities today and desired

Widely Available Clinical Capability	Today (%)	Desired in 3-5 Years (%)
Pharmacogenomics	11	56
Germline Sequencing	11	17
Tumor Sequencing	11	29
Rare Disease Diagnosis	6	17
Microbial Pathogen Identification	11	53
Systematic Family History	46	71
Genetic Counselors	30	77
Electronic Medical Record	30	94
Clinical Decision Support	33	94

< 33% 34-66% > 66%

What are the challenges? -1



What are the challenges? -2

- Quality of data and analysis: what is the indication? Whole genome versus targeted. Beyond SNVs. identifying and using modifier variants
- What is an actionable variant? for the indication; incidental findings
- Understanding and interpreting variants
- Engaging patients: satisfaction, expectations, incidental findings. Privacy; consent
- Potential for poor and costly care if sequencing introduced inappropriately

What are the challenges? -3

- outcomes (including cost effectiveness)
- diverse ancestries
- training
- expand scope to non-academic clinical settings
- implementation and integration in EMR environments
- mechanics of information generation and delivery; e.g. interacting with CAP
- need for large datasets linking genotypes and phenotypes
- Interfacing with regulators (e.g. FDA) and payers

If NHGRI doesn't take coordinated action, the promise of genomic medicine will be delayed

NHGRI imperatives – maximize benefit/minimize risk

- which patients, which targets.
- analysis of genomes for discovery and implementation
- accrual of Large genotype-phenotype datasets across ancestries to understand variant function
- work out the realities of implementation: consenting, EHR integration, patient and provider education, clinical decision support, follow-up…
- promoting analysis of economic and health outcomes