Teaching genomics

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From then to now…

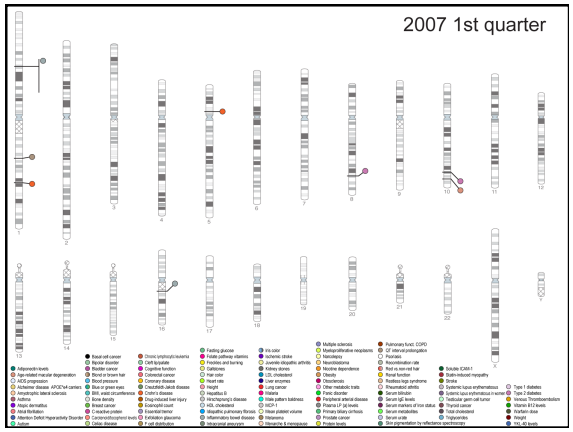
- Rare, serious
- Mendelian
- Highly penetrant
- Few genetic tests
- Based on FHx or ethnicity

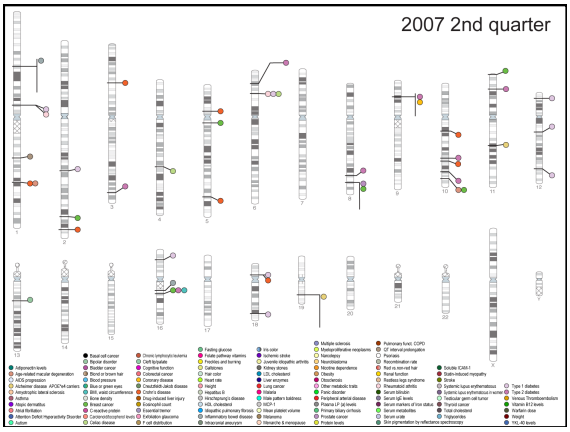
- Thousands of genetic tests
- Testing panels
- Still start with a differential dx, triage testing till a diagnosis found
- Predictive testing often available
- Slow clinical incorporation in many areas (e.g. GWAs, pharmacogenomics) d/t limited evidence base

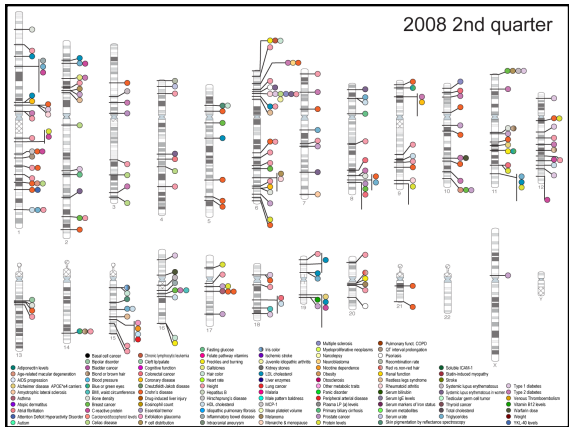
- WES/WGS as a technique and a test
- Analytic and clinical validity
- Often used after other tests negative
- 'Incidental' findings

- Few GCs or geneticists
- Mostly practicing in pediatrics or OB

- ~3700 GCs and 1400 geneticists certified in US since 1982
- Expanded into many specialties (oncology, cardio, neuro, psych, etc.)
- Lab and Industry GCs
- Growing international presence in clinical genetics







DTC Genomic Testing

Best Inventions of 2008

The Retail DNA Test

TIME

PATHWAY GENOMICS®

deCODE genetics

Navigenics

23andMe

What if your 'patient' is Steve Quake, and he sequences his own genome?

Clinical assessment incorporating a personal genome

Evan 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, Normal F Neff, Lavanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Walt Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

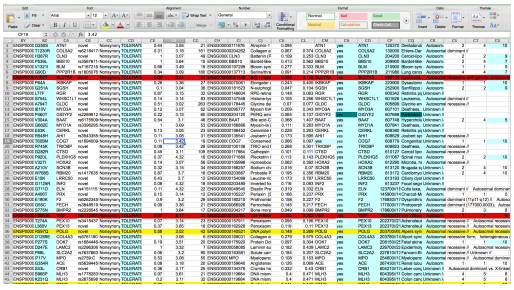
Summary

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.

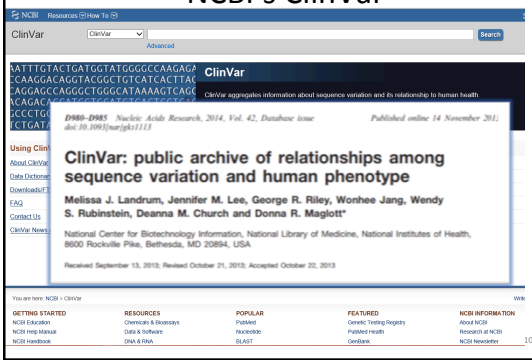
Lancet 2010; 375: 1525–35

See Comment page 1497

What am I supposed to do with this?



NCBI's ClinVar



ClinVar

ClinVar: public archive of relationships among sequence variation and human phenotype

Melissa J. Landrum, Jennifer M. Lee, George R. Riley, Wonhee Jang, Wendy S. Rubinstein, Deanna M. Church and Donna R. Maglott*

National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Bethesda, MD 20894, USA

Received September 13, 2013; Revised October 21, 2013; Accepted October 22, 2013

The future: WGS on healthy individuals

Clinical assessment incorporating a personal genome

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See Comment page 1497

Challenges in the clinical application of whole-genome sequencing

Kelly E Ormond, Matthew T Wheeler, Lavanne Hudgins, Teri E Klein, Atul J Butte, Russ B Altman, Evan A Ashley, Henry T Greely

As the cost of sequencing the human genome falls, or more serious diseases. For example, a patient could

Lancet 2010; 375: 1749–51

OPEN ACCESS Freely available online

PLOS GENETICS

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

Frederick E. Dewey[1], Rong Chen[2], Sergio P. Cordero[3], Kelly E. Ormond[4,5], Colleen Caleshu[1], Konrad J. Karczewski[3,6], Michelle Whirl-Carrillo[4], Matthew T. Wheeler[1], Joel T. Dudley[2,7], Jake K. Byrnes[8], Omar E. Cornejo[9], Joshua W. Knowles[1], Mark Woon[4], Katrin Sangkuhl[4], Li Gong[4], Caroline F. Thorn[4], Joan M. Hebert[4], Emidio Capriotti[10], Sean P. David[1], Aleksandra Pavlovic[1], Anna West[4], Joseph V. Thakuria[11], Madeleine P. Ball[2], Alexander W. Zaranek[2], Heidi L. Rehm[5], George M. Church[2], John S. West[12], Carlos D. Bustamante[4], Michael Snyder[4], Russ B. Altman[4,13], Teri E. Klein[4], Atul J. Butte[4], Euan A. Ashley[1]*

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Molecular Genetics & Genomic Medicine
Open Access
INVITED COMMENTARY

From genetic counseling to "genomic counseling"

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J Genet Counsel
DOI 10.1007/s10897-014-9689-4
NEXT GENERATION GENETIC COUNSELING

Teaching Genomic Counseling: Preparing the Genetic Counseling Workforce for the Genomic Era

Gillian W. Hooker · Kelly E. Ormond · Kevin Sweet · Barbara B. Biesecker

Received: 29 June 2013 / Accepted: 9 January 2014

What were programs teaching in 2011/2012?

Table 1 Integration of genomics into training program curricula of 17 genetic counseling training programs, based on survey data

	Status in training programs, n (%)			Formal curriculum, n (%)		Informal curriculum, n (%)			
	Currently taught	Under development	Will not be taught	Course lectures	Required guest lectures	Optional guest lectures	Professional meetings	Clinical rotations	Journal clubs
Genomic technologies	15 (88 %)	2 (12 %)	0 (0 %)	17 (100 %)	8 (47 %)	5 (29 %)	11 (65 %)	8 (47 %)	15 (88 %)
GWAS	14 (82 %)	2 (12 %)	1 (6 %)	15 (88 %)	5 (29 %)	5 (29 %)	9 (53 %)	7 (41 %)	11 (65 %)
Complex disease genetics	15 (88 %)	1 (6 %)	1 (6 %)	15 (88 %)	8 (47 %)	7 (41 %)	8 (47 %)	10 (59 %)	11 (65 %)
DTC/SNP[a]	11 (73 %)	4 (27 %)	0 (0 %)	10 (59 %)	4 (24 %)	5 (29 %)	10 (59 %)	4 (24 %)	10 (59 %)
Pharmacogenomics[b]	13 (81 %)	3 (19 %)	0 (0 %)	14 (82 %)	3 (18 %)	3 (18 %)	8 (47 %)	2 (12 %)	7 (41 %)
Genomic counseling	12 (71 %)	5 (29 %)	0 (0 %)	13 (76 %)	5 (29 %)	3 (18 %)	11 (65 %)	11 (65 %)	9 (53 %)

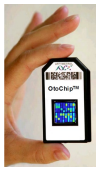
Topics are listed here in the order that they were listed on the survey
[a] Only 15 participants responded regarding DTC/SNP, therefore, the percentage is n/15 for this topic
[b] Only 16 participants responded regarding pharmacogenomics, therefore, the percentage is n/16 for this topic

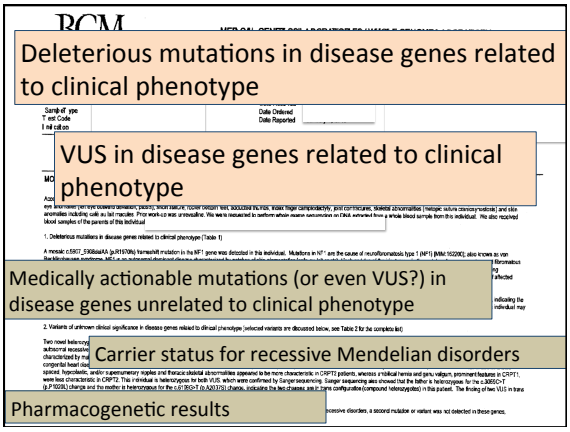
Ways we do it

- Molecular genetics curriculum
- Informal learning (journal clubs, department talks, grand rounds)
- Role modeling involvement
- Variant interpretation rotation – required
- Research project focus

Testing 'Panels'

- **Chip based approaches to examine a range of genes**
  - Examine common mutations vs.
  - Sequencing based technologies
- **Especially helpful when a disorder has significant locus heterogeneity that cannot be clinically differentiated or have significant overlap**
- **Experienced clinicians may find ordering targeted testing more sensitive and specific**
- **Currently available examples**
  - Nonsyndromic hearing loss
  - Cardiology (cardiomyopathy, arrhythmias, other CV disorders)
  - RAS-opathies
  - Mitochondrial disease
  - Cancers
  - Autism spectrum
  - Severe combined immunodeficiency
  - X linked Intellectual disability
  - Carrier testing





Variant interpretation

- Required since graduating class of 2013
- Students complete 20-100 variants
- Learn about underlying bioinformatics, databases for variant interpretation
- 'walk through a genome'

Getting up to speed interpreting genomes

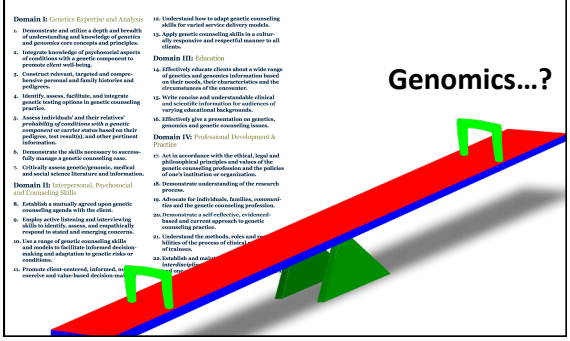
- Technology:
  - Limitations of various platforms, areas of the genome
  - General principles: base calling, alignment, error rates
- Classic concepts of inheritance and the impact of mutation types
- Bioinformatics assumptions and limitations
  - Conservation modeling
  - Inheritance modeling
  - Pipeline assumptions
  - Variant and splice site predictors
- Manual processes and available databases
  - OMIM, HGMD, ClinVar, dbSNP, 1000 genomes, LOVD, etc…
-

Hooker et al. (JGC, 2014)

'Rotation' goals

- **At the end of this rotation, you will understand:**
- The different contexts in which WGS and WES are currently being applied in a research setting
- How to research and classify potentially disease causing variants found through sequencing technologies
- The differences in approaches to variant identification and curation for healthy individuals as opposed to individuals with a likely genetic disease
- Ethical and counseling issues involved in whole-genome sequencing including special considerations for consent, privacy, information storage and updates, genomic literacy and return of results
-
- **You will be expected to be able to:**
- Demonstrate knowledge of genome sequencing technology and the bioinformatics pipelines used to call and classify the variants
- Develop expertise in using various variant annotation genome databases including NHLBI ESP, ExAC, 1000Genomes, ClinVar, HGMD, dbSNP, UCSC, Polyphen, SIFT, mutation taster, and various locus specific databases to clinically interpret variants
- Demonstrate knowledge of various considerations involved in consenting individuals for WES/WGS in a research environment
- Go through the process of analyzing a healthy participant exome for variants likely to be medically relevant, and return results back to the participant

Balancing many curricular needs



ACGC Competencies 2015

Domain I: Genetics Expertise and Analysis

1. **Demonstrate and utilize a depth and breadth of understanding and knowledge of *genetics* and *genomics* core concepts and principles.**
2. **Integrate knowledge of psychosocial aspects of conditions with a genetic component to promote *client* well-being.**
3. **Construct relevant, targeted and comprehensive personal and family histories and pedigrees.**
4. **Identify, assess, facilitate, and integrate genetic testing options in genetic counseling practice.**
5. **Assess individuals' and their relatives' *probability of conditions with a genetic component* or carrier status based on their pedigree, test result(s), and other pertinent information.**
6. **Demonstrate the skills necessary to successfully manage a genetic counseling case.**
7. **Critically assess genetic/genomic, medical and social science literature and information.**