Sequencing in large samples: Consent, data access, ability to recontact

UW Medical Genetics f. 1957

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Where are the debates?

1) Consent models and access
   - Informed consent vs. opt out vs. anonymous.
   - Is recontact needed?
   - What is appropriate consent language?
   - Broad consent vs. narrow consent?
   - Is all data broadly shared?

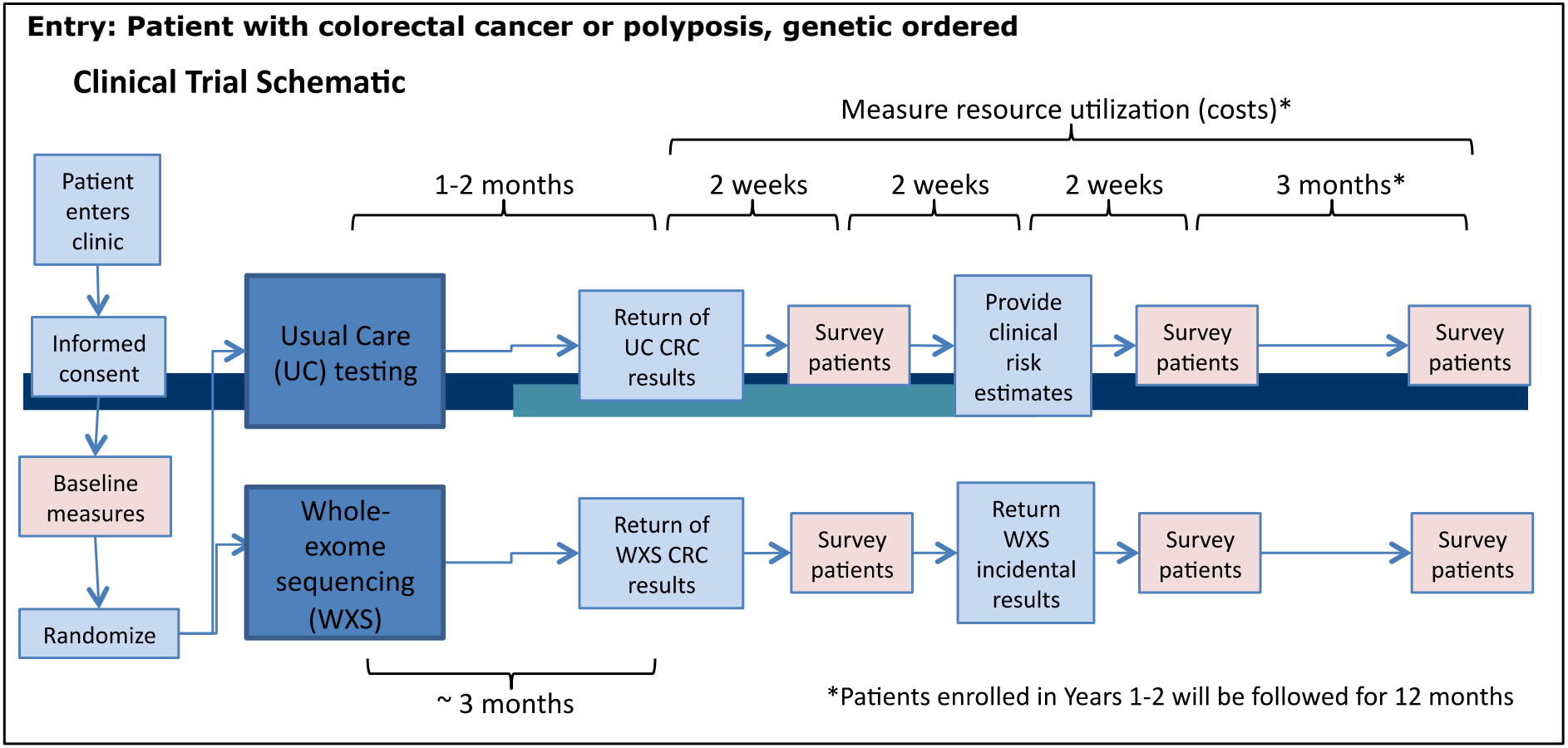
2) Recontact and Return of Results
   - Value of recontact
   - What is actionable?
   - Can you ethically not return actionable data?
   - Do you need to look for actionable data?
   - Many people will want "all" data.
   - Can subjects refuse to get actionable data
   - Do you give adult onset actionable findings to kids?

Consent models for large cohorts

- Full informed consent has advantages

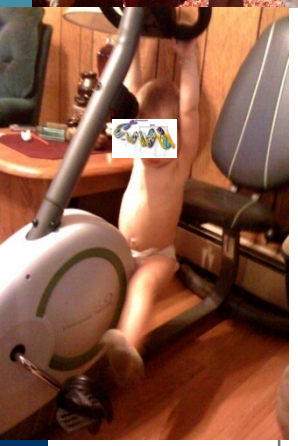
	Full informed consent	Anonymize, opt out
Broad data sharing	+	+
Recontact	+	-
Collect additional phenotypes	+	+/-
Return results	+	-
Incorporate genomics into care	+	-

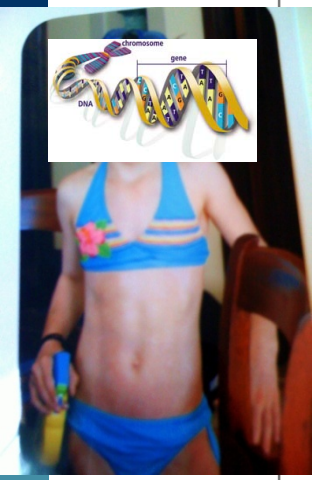
UW CSER UO1: RCT of exomes in CRC/P

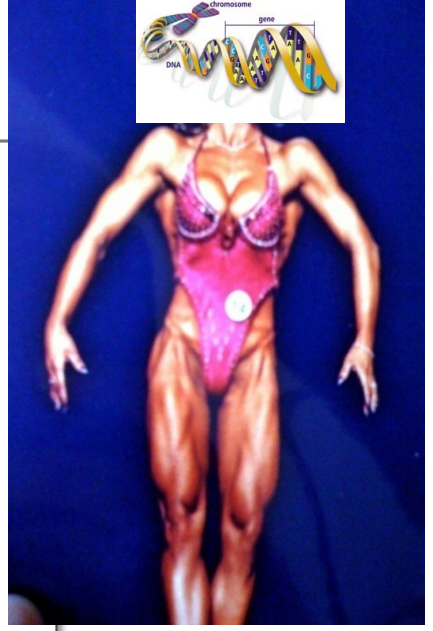


Identified subject with an HGMD pathogenic mutation in an arrhythmia gene

Recontact: The buff gene







5′6″
8 83 yrs

4′11″
Cherokee

Mixed European

63 y.

4′10″

4′10″
33 y.

5′7″

Called Incredible Hulk.

4′11″
19 y.

5′7″
17 y.

11 y.

1 y.

Muscular

Strong

Shorter?

Normal lifespan

Key
= affected female
= affected male
= unaffected female
= unaffected male
= deceased male
= identical twins

Exome variant server LDLR query

http//evs.gs.washington.edu/EVS/

Gene Name: LDLR

Gene ID: 3949

Chromosome 19: 11200038 - 11244506 (+)

Population: EuropeanAmerican, AfricanAmerican

Variation Color Code:

splice or nonsense or frameshift

missense

coding-synonymous

coding

utr

Download Option:

File Format: Text

Zip Format: gzip

download

Add or Remove Columns (Description of Columns)

☑ dbSNP rs ID	☑ Alleles	☑ EA Allele Count	☑ AA Allele Count	☑ Allele Count	☑ Sample Read Depth	☐ MAF (%)
☑ Genes	☑ Gene Accession #	☑ GVS Function	☑ Amino Acid	☑ Protein Position	☐ cDNA Position	☐ NCBI 37 Allele
☐ Chimp Allele	☐ Conservation (phastCons)	☑ Conservation (GERP)	☑ Grantham Score	☐ PolyPhen Prediction	☑ Clinical Link	☐ Filter Status
☐ EA Genotype Count	☐ AA Genotype Count	☐ Genotype Count	☑ Illumina HumanExome Chip			

Sort SNPs by SNP Pos

reset

SNP Pos	rs ID	Alleles	EA Allele #	AA Allele #	All Allele #	Avg. Sample Read Depth	Genes	mRNA Accession #	GVS Function	Amino Acid	Protein Pos.	Conservation (GERP)	Grantham Score	Clinical Link	On Illumin HumanExor Chip
19:11200177	unknown	G/A	G=0/A=7018	G=1/A=3737	G=1/A=10755	26	LDLR	NM_001195803.1	utr-5	none	NA	-3.8	NA	unknown	no

-Exome/genome variant server FABULOUS for allele frequencies

-But, I cannot find out of the people with my variant have the buff phenotype

-Likely NOT in their medical record; thus, I need recontact

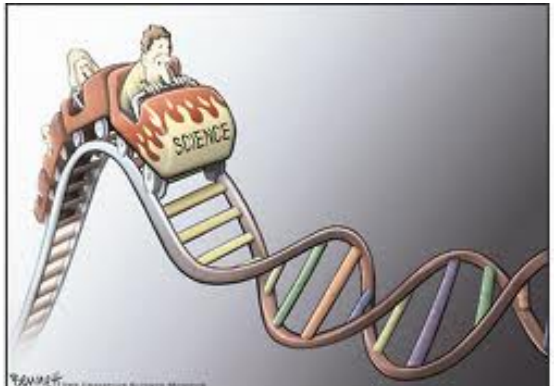
Informed consent: study view

- Understand subject needs
- Explain data being generated, broad future studies
- Consent to broad study goals and data-sharing
- Consent to recontact
- Offer return of genetic results
  - Primary, if relevant
  - Incidental (Not secondary) Explain that the our understanding of the genome is evolving
  - Address survivorship

Informed consent: subject view

- Benefits (return dependent)
  - Prevention or early diagnosis / treatment of disease
  - Pharmacogenetics to maximize safe and effective drug choices
- Risks (return independent)
  - Privacy (common rule may redefine genetic data as id)
  - False security
- Risks (return dependent)
  - Social / emotional risks
  - Life and long-term care insurance?

    -GINA law protects medical insurance
  - Incomplete penetrance
  - Misclassification of variant
  - Misinterpretation of VUS or benign
  - Cost of follow-up?



Subjects: "Glad you asked"

- Re-consent study invited first 400 mail consenters to participate in telephone interview
- 90% of participants said it was important that they were asked permission for data sharing
  - 69% rated it "very important"
  - 21% "somewhat important"

Ludman et al (2010) *JERHRE*
Trinidad et al (2011) *Science* 21; 331:287-8

Acceptability of alternatives

Subject Role/View	Completely unacceptable	Somewhat unacceptable
Opt-out (Let us know if you don't want your info shared)	19%	21%
	40%	
Notification-only (We already shared it, fyi)	47%	20%
	67%	
No consent, no notification	54%	16%
	70%	

Ludman et al (2010) *JERHRE*

What do people want?

- Public support for return of results
  - NYT's Gina Kolada to weigh in
  - Many expect return even if consented to none
- Focus group participants are highly motivated and educated
- What do people that are less engaged want?
  - Best case?: Family study, last contact within 10 years, contact by mail only:
    - 1/234 decline of broad reconsent
    - 21 lost to follow-up
    - 212 signed and returned reconsent (91%)

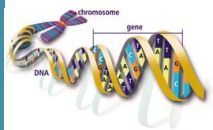
Worst case reconsent success rate?

Veterans seen once, up to 20 years ago

	addendum returned and agreed to dbGaP posting	addendum returned and Declined dbGaP posting	Not interested per phone call	addendum not returned lost/ignored still working on following up	Total
Total	872	79	124	655	1730
% of mailing group (n=1730)	**872 (50%)**	**79 (5%)**	**124 (7%)**	**655 (38%)**	1730 (100%)
% male	555 (64%)	42 (53%)	91 (73%)	420 (64%)	1108 (64%)
% WNHO	682 (78%)	57 (72%)	81 (65%)	438 (67%)	1258 (73%)
% Asian	102 (12%)	11 (14%)	14 (11%)	84 (13%)	211 (12%)
%BNHO	55 (6%)	3 (4%)	**21 (17%)**	91 (14%)	170 (10%)
% Hispanic	20 (2%)	3 (4%)	4 (3%)	25 (4%)	52 (3%)
% Native American	13 (%2)	5 (6%)	4 (3%)	17 (3%)	39 (2%)
age range (mean)	37-97 (72)	54-87 (68)	56-93 (74)	29-95 (68)	29-97 (71)
% Vet	446 (51%)	39 (49%)	83 (67%)	360 (55%)	928 (54%)
declined both dbGap and Cell-lines	N/A	58 (83%) (n=70)	N/A	N/A	N/A
% declined Cell-lines yes to dbGaP	3 (0.4%) (n=721)	N/A	N/A	N/A	N/A

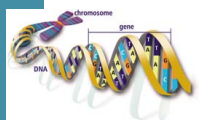
Return of results to kids and adults

- Should consent for ROR—never mandatory
  - Particularly relevant to incidental findings
  - World Med Assoc Helsinki: "right to self-determination"
  - Autonomy and Subsidiarity (do not take decisions away)
- Context dependence of actionable variants
  - Adults are past risk for pediatric onset conditions
  - Adult onset disease in a kids is a separate issue
    - Autonomy: Do not order tests for adult onset disease in kids
    - Differs when these are incidental findings of a genome test
    - Beneficence: seek the patients good
    - Justice: Rights of parent who transmitted the allele
- Return of incidental findings in an ill patient
  - May prefer not to have these during a critical illness
  - Consent to return to family in case of death



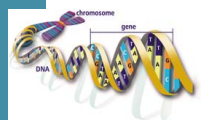
Data access

- Advocate broad data access
  - Demonstrated utility in eMERGE and ESP/EVS, among other projects
  - Many expect return even if consented to none
- Public is wary of commercial access and government control
- Exceptions? Minority populations, yet these data are most needed
- Impact of changes to common rule?
  - If genetic data is considered identifable



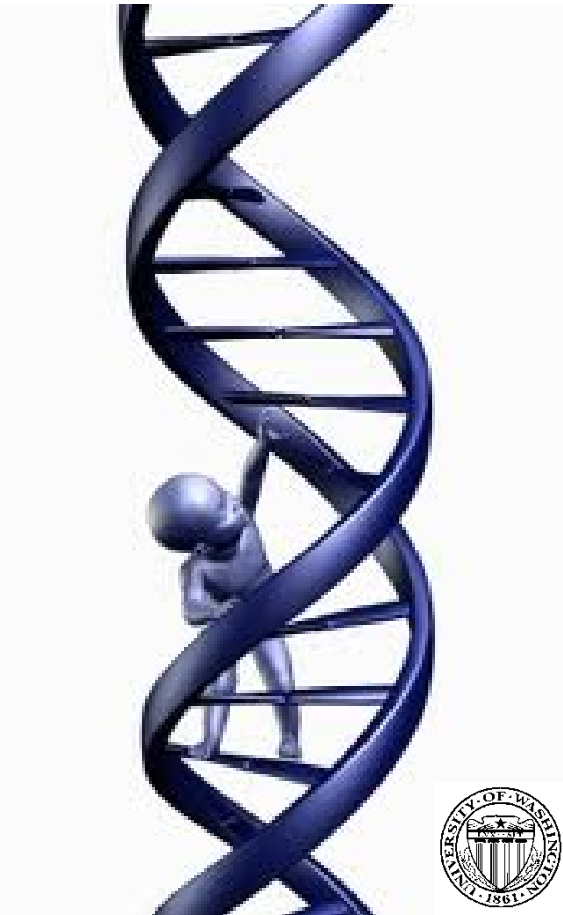
Questions

- Who needs screening colonoscopy at
  - 40 years old?
  - 50 years old?
  - 60 years old?
- Can we predict who has celiac?
- Theme: Change medical system behavior



Conclusions

1. Consent
   a) Identified, recontactable subjects are optimal for the sequencing age
   b) Allow opt out of return of genomic results
   c) Consents should be shorter, but complete
   d) Consent language will evolve
2. Data access should be broad
3. Recontact and return of results
   a) Recontact increases utility
   b) Return of significant actionable findings
   c) Develop consensus on these
   d) We may not all agree on what is best
      - What genes to return (and to whom)
      - Pediatric return of adult onset



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SPECIAL ARTICLE | Genetics inMedicine

Exploring concordance and discordance for return of incidental findings from clinical sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Gerard T. Berry, MD[4,5], Leslie G. Biesecker, MD[6], David P. Dimmock, MD[7], James P. Evans, MD, PhD[3], Wayne W. Grody, MD, PhD[8–10], Madhuri R. Hegde, PhD[11], Sarah Kalia, ScM[1], Bruce R. Korf, MD, PhD[12], Ian Krantz, MD[13], Amy L. McGuire, JD, PhD[14], David T. Miller, MD, PhD[4,15], Michael F. Murray, MD[1,2], Robert L. Nussbaum, MD[16], Sharon E. Plon, MD, PhD[17,18], Heidi L. Rehm, PhD[2,19] and Howard J. Jacob, PhD[7,20]

Purpose: The aim of this study was to explore specific conditions and types of genetic variants that specialists in genetics recommend should be returned as incidental findings in clinical sequencing.

Methods: Sixteen specialists in clinical genetics and/or molecular medicine selected variants in 99 common conditions to return to the ordering physician if discovered incidentally through whole-genome sequencing. For most conditions, the specialists independently considered three molecular scenarios for both adults and minor children: a known pathogenic mutation, a truncating variant presumed pathogenic (where other truncating variants are known to be pathogenic), and a missense variant predicted *in silico* to be pathogenic.

Results: On average, for adults and children, respectively, each specialist selected 83.5 and 79.0 conditions or genes of 99 in the known pathogenic mutation categories, 57.0 and 53.5 of 72 in the truncating variant categories, and 33.4 and 29.7 of 72 in the missense variant categories. Concordance in favor of disclosure within the adult/known pathogenic mutation category was 100% for 21 conditions or genes and 80% or higher for 64 conditions or genes.

Conclusion: Specialists were highly concordant for the return of findings for 64 conditions or genes if discovered incidentally during whole-exome sequencing or whole-genome sequencing.

Genet Med advance online publication 15 March 2012

Key Words: incidental findings; whole-exome sequencing; whole-genome sequencing

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