GENE30005 Human and Medical Genetics **[Notes]**

L1 Personalomics: Genetic Variation in the Human Genome

Can get a personal genome sequence & SNP genotyped (Variants across genome characterised).

SNP Typing: Illumina Applications: Genotyping: 200 ng, 730000 markers. Illumina Omni Express Bead Chip.

- In each well: silica beads in **microarray**, each bead has unique primer sequences with SNP.
- SNPs in human genome are given an rs number to identify the polymorphism.
- A primary extension reaction occurs: 4 nt different dyes: **score homo/heterozygotes from bases incorporated**.

Ancestry: Chromosome painting: Estimated heritage of that part of genome. Get an idea of **deep history**.

Neanderthal & Me: Fraction of your genome that is Neanderthal.

Genotype & interpretation direct to the consumer: 23andMe, Pathway Genomics, Navigenics, deCODEme.

- Health predictions offered in 2012 from e.g. 23andMe.
- Disease Risk: List of potentially genetic determined conditions/influences: Compared to ave risk of the population.
- Carrier? May be able determine if an individual is a carrier for a disease.
- Drug response: *Important reason why personalomics is of interest. Different people metabolise e.g. warfarin (blood thinner) ∴ would be ideal to be able to administer the correct dosage for an individual if you knew their genotype, rather than experimentally determining it on the individual until symptoms or not were shown.

Can these companies be trusted to genotype & interpret data accurately? 2010 US "Government Accountability Office" submitted same DNA to 4 companies: Completely different results (discrepancies), all consistent with medical histories. Across three different companies:

- Each score a different set of genetic variants, & give different variants different risk factors towards diseases.
- **Do not** always agree (i.e. not 1:1 correlation) e.g. Crohns have little correlation between deCODEme & 23andMe.
- deCODEme has a risk of greater than 150%: give false answers.
- Led to people to enforce they are **not** allowed to give advice or health advice can be provided.

Q: BRCA1/BRCA disease alleles? A: VUS: Variant of Uncertain Significance: Advice may **not** be satisfying for individual.

Community Phenotyping: "PatientsLikeMe"; Citizen scientists; Patient advocacy groups; Research participants: Biochemical assays, biopsies; Patients know their history.

- Individuals with **rare** diseases in families: would like to know more about it.
- By sharing their genome they aim to provide those with the ability to possibly cure the disease.
- MyGene: Easy for families with rare conditions, doctors & researchers to share data publically & equitably.

Personal genome Project: Approach from Harvard University, share an open data where your open genome & complete medical records are entered into this record, this data is used to characterised genetic diseases & conditions.

Even if companies accurately interpret the data appropriately, do we understand what genetic risk is? People want genetic tests to be like pregnancy test, Klitzman explains: "You're either pregnant or you're not. Instead they're more like a weather report." And most people aren't prepared to cope with the probabilities & uncertainties that entails. This is a vital question. People need to know how to interpret the findings.

How will consumers deal with the fact that: 8% of us will have genetic disorder recognised upon reaching adulthood.

Is society ready?

- Can it deal with the scientific uncertainty? What is the clinical utility of a given genotype?
- Will the knowledge improve clinical outcomes? Will it lead to further tests that over-burden health care system?
- "Results clearly show that these tests are not ready for prime time": Gregory Kutz.
- **US FDA directs that health related reports are not offered until a review has been carried out**.

OMIM (Online Mendelian Inheritance in Man): An online catalog of human genes & genetic disorders.

Drug Response: Warfarin: CYP2C9: Which allelic variants are important? ARG144CYS reduced warfarin metabolism; rs1799853 SNP; Other variants affecting warfarin resistance: OMIM entry on Cyp2C9 tells us VKORC1 gene is important.

- A problem with genome testing **is how to combine both forms of information**.
- How much **epistasis**/interaction between variants are there in order to develop phenotype/condition.
- ∴ Fundamental reason different companies display different risks.
- The more complicated a disease is the more difficult the risk analysis or confidence is.

How do you assess health risk?

- How do you combine all variants affecting a trait together? Which SNPs, what algorithms? Do they interact in an additive way? If we don't know, is it safe to assume they do?
- What about un-scored functional variants? Ethnic bias in what we know & what is typed. Unscored variants could be protective or deleterious.
- Need to be quantitative: understand probability

Privacy: Anonymous? Genomes -> names -> address & age, internet data -> medical records, insurance issues

- Rare variants: could identify you as a participant in a large pooled study
- Your data provides information about your relatives

Prof. Michael Snyder's 'omics: Integrated Personal -omics Profile (iPOP)

- Peripheral blood monocytes, serum & plasma: transcriptome, proteome, metabolome, cytokines & antibodies.
- Monitored 40,000 components over time including two viral infections
- His genome to reference genome: 3 million differences, 10,000s (AA) missense & 73 nonsense mutations.
- Many private SNVs (**only seen in his dataset** & nothing else in the data displays this) & 2,500 structural variants.