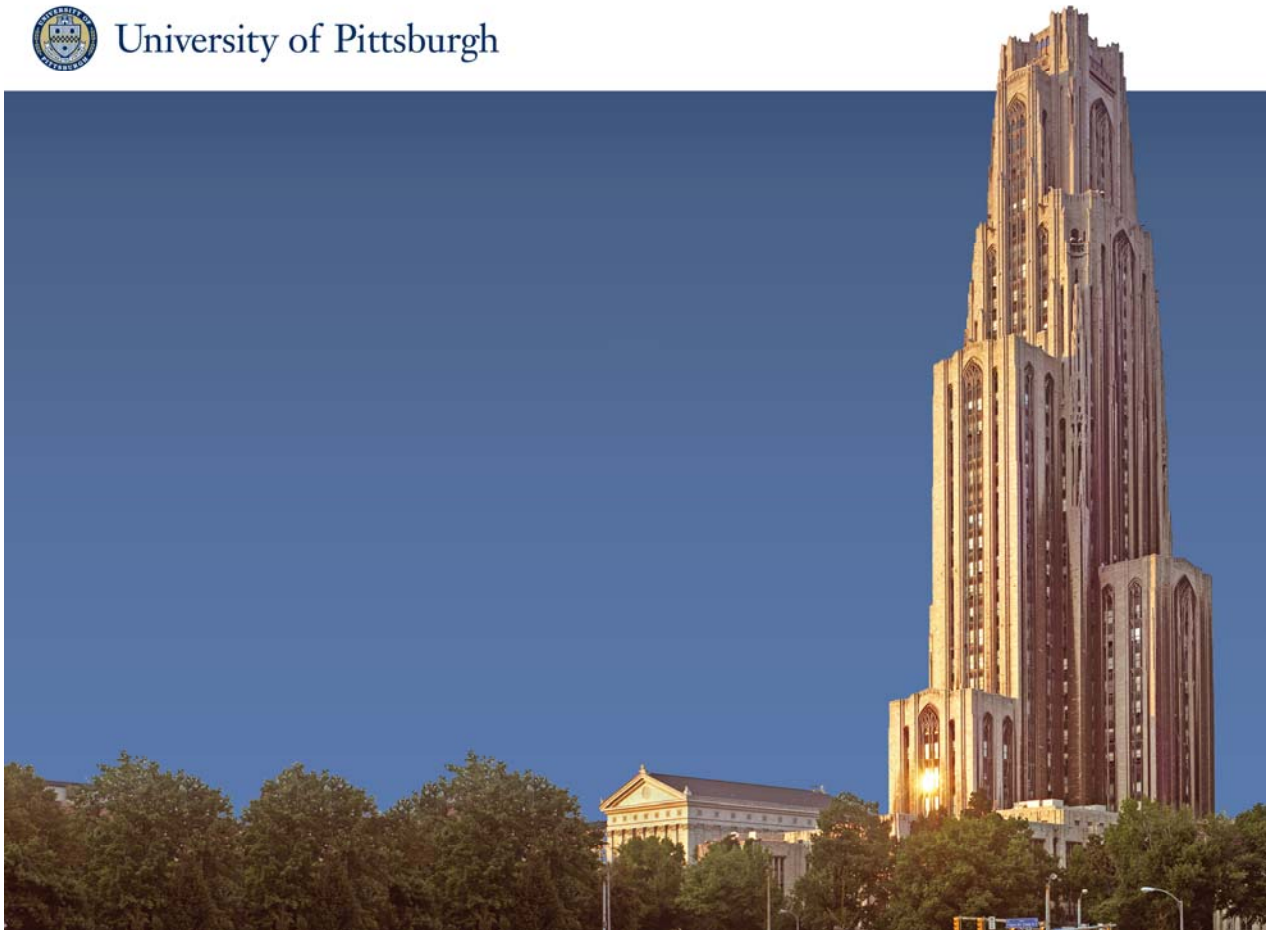
University of Pittsburgh



# What we will cover during this webcast:

Briefly discuss the approaches introduced in the paper:

- Genome Sequencing
- Genome Wide Association Studies
- Epigenomics
- Gene Expression Profiling

Implications for Nursing Practice and Research

Online Databases and Resources

Questions and Answer Session with Attendees

# Genome Sequencing

DNA sequencing → determining the order of nucleotide bases in DNA

Past → methods collected data one base at a time for a focused piece of DNA → still useful today but...

Now → can sequence many pieces of DNA in parallel and covering the entire genome is possible

→ referred to as Next-Generation Sequencing (NGS) or Massively parallel sequencing

Advances in technology have made this possible and the result is we can have greater sequencing coverage of the genome and with reduced cost and time → this makes genome sequencing more appealing for research and clinical utility

# Genome Sequencing

Whole Genome Sequencing (WGS) → sequencing of the entire genome

Whole Exome Sequencing (WES) → sequencing only the coding regions of the genome → exome represents ~1% of the genome but likely to contain ~85% of variability influencing disease

Most phenotypes of interest to clinicians and researchers have more than one gene and more than one variant/mutation influencing that phenotype…WGS and WES can capture these

Captures rare and common variation

# Genome Sequencing

## Power and limitations

### Error rate (~0.5% - 2%)

- Different NGS platforms yield different error rates
- Important that the lab report genes/exons/regions that were not adequately assessed due to missing data or data that the lab deems not of high enough quality
- NGS is a newer technology so it is recommended that findings be confirmed using more validated technology

### Incidental findings

- While looking for variation involved with a specific phenotype it is very possible that variation of clinical importance not related to the index phenotype will be uncovered...

# Genome-Wide Association Studies (GWAS)

Genome Wide = genotype data collected for polymorphisms that span the entire genome

Association = relationship between two variables (in this case genotype and phenotype) that makes them statistically dependent

At the most basic level, one would analyze each polymorphism for association with the phenotype of interest; however it is noteworthy that more sophisticated analyses are possible (for example gene-gene interactions; pathway analyses)

# Genome-Wide Association Studies (GWAS)

Single nucleotide polymorphisms (SNPs) are the most frequently used polymorphism for a GWAS and the number of SNPs investigated often varies between 500,000 – 2,000,000.

Variation within a SNP captures variation for surrounding genomic region (extent of region differs across the genome) → Linkage disequilibrium

Most common design is case - control

# Genome-Wide Association Studies (GWAS)

Greatest advantage → non-parametric approach

So many phenotypes of interest are not well understood biologically so *a priori* selection of genes to investigate may not be well-informed so this method is amenable to letting the data tell you what gene(s) are likely to be important to the phenotype

# Genome-Wide Association Studies (GWAS)

Some important considerations that may be drawbacks to a GWAS

- Requires large numbers of subjects
- Focus is on common variants
- Association → may not have actual DNA change responsible for the relationship…you're close…but work not done

Candidate gene investigation

# Gene Expression Profiling

All genes are in all cells...but not all genes are expressed in all cells

Genes that are differentially expressed when comparing phenotypes of interest can be helpful in uncovering the underlying biology of that phenotype

These differentially expressed genes, after reliability and validity are established, can be used to characterize the phenotype of a tissue that can be useful clinically (risk stratification, etc)

Phenotypes of interest can be presence/absence using case – control design (comparing groups of individuals with and without a phenotype of interest) or at the cellular level within an individual (comparing healthy to unhealthy tissue)

# Gene Expression Profiling

Relies on evaluation of RNA

DNA → mRNA → protein

Like GWAS, there are approaches available that allow one to look at extent of gene expression for each gene across the entire genome

At the most basic level, one would analyze level of expression for each RNA assessed for association with the phenotype of interest; however it is noteworthy that more sophisticated analyses are possible (for example gene-gene interactions; pathway analyses)

# Gene Expression Profiling

microRNA (miRNA) are small RNAs involved in gene regulation by binding to mRNA impacting it's ability to be translated into a protein

Expression of miRNAs can be evaluated and are often incorporated into whole genome gene expression data collections

Whole genome expression has similar advantage to GWAS → allows for a non-parametric approach

RNA is not DNA...

# Epigenomics

Back to DNA – but not interested in the nucleotides (like sequencing and GWAS) but instead how the DNA is chemically modified or packaged

The chemical modifications and packaging impact whether a gene is expressed → mechanism behind gene expression

Types include histone modifications; chromatin structure; non-coding RNAs; DNA methylation

# Epigenomics

DNA methylation – addition of methyl groups (chemical modification) to a GC rich region of DNA

Hypermethylation = gene shut down – no expression

Hypomethylation of a gene that is suppose to be methylated results in activation of that gene

# Epigenomics

Shares some methodological issues with DNA polymorphism-based approaches as well as RNA-based approaches

DNA is template of interest → stable BUT methylation pattern of genes differs by tissue type and can be impacted by exposures (endogenous and exogenous)

Like GWAS and whole genome expression profiling, there are approaches available that allow one to look at extent of methylation across the entire genome = methylome; therefore allowing for a non-parametric evaluation

Other advantages → dynamic and mechanistic

# Implications for Nursing Practice and Research

Table 1. Current and Emerging Genomic Approaches: Outcomes and Implications for Health Care

| | Approach | | | |
|---|---|---|---|---|
| | Genome sequencing | Genome-wide association studies | Gene expression profiling | Epigenomics |
| Outcomes | Greater volumes of information processed faster and more cheaply, facilitating whole-genome sequencing, with accelerated scale and pace of gene discovery. | Genetic variation between those with and without a specific disease identified through large population studies. | Insights into the role of differential gene expression in normal biological and disease processes. | Growing understanding of gene-environment interaction and influence on gene activity not involving the DNA sequence itself. |
| Clinical implications and possibilities | More accurate and cost-effective diagnosis and genetic testing; earlier detection of disease and of those at risk for disease; antenatal testing using cell-free fetal DNA; pharmacogenomics; tissue typing and transplantation; rapid response to infectious disease outbreaks through pathogen sequencing. | Greater knowledge of gene loci associated with a broad spectrum of diseases; helps identify genetic contribution to risk. Identifying genetic component(s) of common complex diseases helps identify potential targets for drug development. | Potential for greater accuracy in diagnosis, individualized prognosis, targeted treatment, and post-treatment surveillance, particularly in oncology. | Potential for manipulating epigenetic gene regulation through modifying environmental factors (e.g., nutrition). Of particular relevance during embryogenesis. |

| | |
|---|---|
| Implications for nursing education, practice, and research | *Education:* Keeping up to date with advancing knowledge and understanding of disease mechanisms; educating others, including patients and their families.<br>*Research:* Recruiting patients to studies; building the evidence base for genomic health care in nursing practice.<br>*Clinical care:* Explaining complex risk; dealing with uncertainty; managing patient expectations; explaining treatment choices and targeted treatment.<br>*Public health nursing:* Managing public expectations of personal consumer genomics; translating epigenetic advances to health promotion and education; translating new knowledge to infectious disease management.<br>*Ethical practice:* Upholding autonomy and informed consent in research studies and genetic screening/testing using fresh and stored DNA; managing the implications of intended and incidental findings of (whole) genome sequencing; upholding privacy and confidentiality.<br>*Nurse leadership*: Leading in the translation of new knowledge and understanding into healthcare practices and pathways; driving policies to implement change in nursing regulation, practice, and education to promote competent, evidence-based and holistic care. |

University of Pittsburgh School of Nursing

# Online Databases and Resources

| | |
|---|---|
| Catalog of Published Genome-Wide Association Studies | http://www.genome.gov/gwastudies |
| Database of Genotypes and Phenotypes (dpGap) | http://www.ncbi.nlm.nih.gov/gap |
| ClinSeq: A Large-Scale Medical Sequencing Clinical Research Pilot Study | http://www.genome.gov/20519355 |
| Gene Expression Omnibus | http://www.ncbi.nlm.nih.gov/geo |
| Cancer Genome Atlas | http://cancergenome.nih.gov |

| | |
|---|---|
| Epigenomics Fact Sheet | http://www.genome.gov/27532724 |
| Epigenomic Datasets | http://www.ncbi.nlm.nih.gov/epigenomics |
| Human Epigenome Project | http://www.epigenome.org |
| Genetic Test Registry (GTR) | http://www.ncbi.nlm.nih.gov/gtr |
| Online Mendelian Inheritance in Man (OMIM) | http://www.ncbi.nlm.nih.gov/Omim |

# Questions?