MEDICAL GENOMICS AND ELECTRONIC HEALTH RECORDS

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Overview

- Brief walk through essential concepts
- The role of health information technology in genomic medicine
  - At the point-of-care
  - For population health management
  - For research
- Privacy considerations

Definitions

- Genomics
  - The functions and interactions of all the genes in the genome
- Medical Genomics
  - The application of our rapidly expanding knowledge of the human genome in healthcare
    - Research
    - Prevention
    - Treatment
  - Information that will allow for patient specific care
    - “Personalized Health Care”
  - A rapidly expanding area of medicine that could result in massive information overload for:
    - Patients
    - Health care providers
    - The insurance industry
    - Health care regulatory bodies

Promise of Genomics

"Genomics based knowledge and tools promise the ability to approach each patient as the biological individual he or she is, thereby radically changing our paradigms and improving efficacy."

- *Guttmacher, et al*

Human Genome Variations

- 99.9 percent of DNA is identical in all people
  - Differences in the remaining 0.1% hold important clues about health and disease
- Over 3 billion base pairs in the human genome
- Two unrelated humans have DNA sequences that vary at millions of these base pairs
  - Variants referred to a “single-nucleotide polymorphisms” (SNPs)
  - Certain SNP patterns correlate with disease, risk of disease, and response to treatments
- SNPs patterns transferred to offspring via haplotypes (sequences of DNA that tend to be inherited together)

Human Genome Project

- Fully sequenced in 2003
  - 30,000 to 35,000 genes identified
    - These genes encode over 100,000 proteins
    - Over 1,000 genes known to have mutations related to diseases
      - Number of disorders with genetic markers rapidly growing
- Has markedly accelerated our understanding of the genetic underpinnings of health and disease

HapMap Project

- Completed in 2005
- A set of associated alleles in a region of a chromosome is called a haplotype
- Most chromosome regions have only a few common haplotypes
  - These tend to be inherited together
- Haplotypes account for most of the variation from person to person in a population
- The HapMap database allows for targeted focus on genetic regions that are likely to affect disease

Genome Wide Association Studies

- Involves rapid scanning of SNP markers across the genome
- Used to find single/groupings of SNPs associated with:
  - A disease (e.g., Parkinson's Disease)
  - An increased risk for a disease
  - Increased risk for a complication from a procedure or associated condition
    - E.g., risk of DVT following surgery
  - Therapeutic responses to interventions (e.g., drugs)
    - Adverse event prevention
    - Increased likelihood of positive response
- Large numbers of patients needed to reach statistical significance

Multigene Inheritance of Common Disorders

- Most single gene mutation inherited disorders are rare
- Common diseases (e.g., diabetes and hypertension) are heavily influenced by multigene expression tied to specific SNP patterns
  - Identifying patterns of SNPs tied to these disorders will:
    - Allow for a better understanding of the underlying mechanisms of disease
    - Identify patients at elevated risk early in life

Medication Strategies Related to Genomics

- Prescribe drugs known to be more effective given the genetic makeup of an individual patient
  - A.K.A. “designer drugs”
- Avoid giving medications to patients that will result in adverse effects
  - E.g., 10-15% patients on the diabetes drug Avandia develop increased fluid volume (and some develop CHF)
  - Genome wide association studies have identified a haplotype with 6 SNPs that are associated with this adverse effect.
  - If this is proven performing genetic screening prior to giving this drug may improve safety and be cost effective

Epigenetics/Epigenomics

- The susceptibility of patients to succumb to or resist a given disease is related to genetics AND environment
- Definition (Epigenetics)
  - Altered expression of genes without changes to the base pair sequence
    - Very important in embryogenesis
  - May allow species to adapt rapidly in response to environmental signals early in life

Epigenetics

- There are a number of tumor suppressor genes known to be inactivated epigenetically in human tumors
- P53 tumor suppressor gene involved with up to 50% of cancers
  - New therapies target the mechanisms of action of this gene's product
  - Impressive results in head and neck cancer trials

Imprinting and Epigenetics

- Individuals have two copies, or alleles, of most genes
- Normally both alleles contribute to the products of an active gene
- With imprinting one copy is turned off epigenetically
  - This amplifies the effect of the one allele
  - If it is dysfunctional there is no counterbalancing affect from the other allele and this can influence the organism.
- Disorders involving dysfunction of imprinted genes are likely to have an epigenetic component

SELECTED LITERATURE REVIEW

Examples of Genomic Studies Related to Disease

Early Breakthrough Cancer Genomics

- Chronic Myeloid Leukemia
  - Fusion of two genes (BCR and ABL) on the Philadelphia chromosome results in formation of a “fusion” protein that plays a role in cancer proliferation
  - (Imatinub mesylate {Gleevec} developed)
    - Binds with enzyme and blocks activity
  - Now used as targeted molecular therapy for CML, gastrointestinal stromal tumors, and other malignancies

Age Related Macular Degeneration

- Three independent GWA studies (in 2005)
- Looked a large sample size of AMD patients
- Found SNPs in allele for in the gene that codes for complement factor H gene
- This knowledge lends itself to:
  - Better understanding of the pathophysiology of AMD
  - Early detection and identification of patients at risk
  - Prevention
  - Treatment strategies at the molecular level
    - Potentially patient specific strategies

Prostate Cancer

- 1 or every 6 men develop prostate cancer but only 1 in 35 who develop prostate cancer die form this disease
- Numerous loci of SNPs identified via GWA studies that are associated with more aggressive forms of the disease
- The relevance of using this to identify patients at risk for developing the more severe forms of this disease are awaiting clinical trials

Case Study: Using Genomics to Identify Populations at Risk for DVT

- A genetic predisposition accounts for an estimated 60% of the risk for deep vein thrombosis (DVT)
- SNP patterns (7 different ones) associated with elevated risk
- Could be used to identify patients at risk for DVT (e.g., post-operatively, post-partum, etc.)

Multiple Sclerosis

- Recently identified SNPs strongly associated with multiple sclerosis using GWA studies
  - SNPs involving the alleles of genes involved with immune regulation have been identified
    - Interleukin-2 receptor gene (*IL2RA*), Interleukin-7 receptor gene (*IL7RA*), and HLD-DRA locus
  - These are felt to correlate with the immune mediated dysfunction associated with this disease
  - These finding may help to:
    - Elucidate the precise etiology of this disease
    - Identify patients genetically at risk
    - Search for epigenetic factors that trigger the disease in only some patients
    - Develop treatment strategies

GENOMIC ERA CHALLENGES

Challenges

- Rapid development of commercially available genetic tests and other genomic technologies will almost certainly outpace both the:
  - Availability of effective interventions for many conditions
  - The health care professional's acquisition of sufficient knowledge to guide their appropriate use

An Update from the American Health Information Community's Personalized Health Care Workgroup; JAMIA April 2008

Challenges to Moving Forward

- "Use of genetic risk information to guide intervention must be justified by data demonstrating improved outcomes, reduced costs, or both."

  Burke et al, 2007

- Consumer access to information will create a great deal of anxiety and possibly to lead to unnecessary tests

Barriers to Clinical Integration of Genomic Medicine (Scheuner et al, 2008)

- Health professionals issues
  - Knowledge
  - Attitudes
  - Beliefs
  - Abilities
- Lack of oversight of genetic testing
- Privacy
- Confidentiality
- Genetic discrimination concerns

Primary Care Challenges

- *"The most important and consistent finding from our literature review is that the primary care workforce, which will be required to be on the front lines of the integration of genomics into the regular practice of medicine, feels woefully underprepared to do so."*
  - *Shauner , et al,* JAMA, March 19, 2008—Vol 299, No. 11 "**Delivery of Genomic Medicine for Common Chronic Adult Diseases"**

Healthcare Professional Issues

- Primary care physicians
  - Will provide the majority of genomic related care
  - Most lack training in genomics
  - Will be asked to make treatment decisions based on new information based on genomic research
- Areas for ongoing education
  - Improve primary care provider's ability to:
    - Counsel patients on genetic conditions
    - Know when to order genomic tests
    - Accurately interpret genetic tests
    - Identify when patients should be referred for genetic consultation

Reliability of Genetic Information for Use in Patient Care

- Much of the available information is not evidence-based
- Often the information:
  - Pertains only to a small percentage of the population
    - E.g., BRC1 and BRC2
  - Is not specific enough to allow informed decisions
  - Has no proven benefit on outcomes
  - Tests and treatments may not be funded by payers or may be very costly
- Huge number of patients needed to identify SNP patterns suggestive of disease

Research Directions

- Once the specific genes and SNPs are indentified that play a role in the disease
  - The way in which the gene is regulated can be studied more closely
    - E.g., Suppressor/Activator roles
  - The protein(s) being expressed or not expressed can be identified
  - The complex interactions between multiple gene products underlying most common diseases can be studied
    - Will require analysis of a huge number of variables the affect gene expression/regulation and protein regulation

Privacy Concerns

- There is concern that genetic information could lead to discrimination
  - By healthcare insurers
  - By employers
- Individuals may not wish genetic information to be shared
  - About themselves
  - About family members
    - E.g., when non-paternity is identified
  - When choosing a mate….

Privacy Concerns

- It may be difficult for patients to fully understand the ramifications of releasing their genetic information
  - Very complex area
  - Obtaining truly informed consent may be difficult
- Is consent needed from relatives?
  - E.g., DNA will reveal alleles inherited from both parents of an individual
- Controls that protect genetic information from being misused are needed
  - E.g., *Genetic Information and Nondiscrimination Act*

Privacy

- Societal implications of knowledge obtained from genomics will raise challenges
- Examples
  - Extremely high risk for incurable disease
    - Do people really want to know?
  - Pattern consistent with mental health conditions
    - E.g., Antisocial personality disorder, Asperger syndrome, dependency risk, etc.
  - Tendencies passed on to children
    - Should child be informed?

ELECTRONIC HEALTH RECORDS AND GENOMICS

A Future Patient Visit

- Clinical Scenario Year: 2020
- Healthy 25-year-old female visits family doctor
  - Provides consent to have her entire genome sequenced
    - Restrictions are placed on how the information can be shared outside of her immediate care needs
  - Her entire genome is sequenced
  - Digital representation of her DNA is stored securely
  - A program scans her DNA for SNP/Haplotype patterns that may be associated with
    - Diseases
    - Other conditions/tendencies

Scenario Continued

- The EHR automatically presents the clinician with:
  - Information that is:
    - Based on evidence based-medicine compliant research
    - Specific to this patient's DNA signature
      - E.g., Longitudinal risk of developing common diseases
  - Treatment options
  - Links to additional information about each associated condition and treatment options

Scenario: EHR's Role

- Several hundred conditions that the patient is at risk for based on her DNA are displayed.
  - The clinician determines that the following 6 require intervention at this visit:
    - Asthma (SNP pattern plus urban environment)
    - Melanoma (SNP pattern plus sunlight exposure)
    - Hypertension (SNP pattern but atherosclerosis already started)
    - Diabetes (SNP pattern but atherosclerosis already started)
    - Middle-life obesity risk (SNP pattern)
    - Elevated stroke/thrombosis risk on BCPs (SNP pattern)

Scenario Continued

- The EHR suggests recommended therapies based on her DNA, demographics, past medical history and exposure history:
  - She is scheduled for pre-diabetic, pre-hypertensive, pre-melanoma, pre-asthmatic and pre-thrombosis management programs
  - She is scheduled for a dermatology consult and then biyearly skin exams
  - She is placed on a medication that alters the epigenetic changes to her DNA that occurred during childhood
    - This reduces her risk of developing adult onset asthma
  - She is taken off her current birth control pill and placed on one that based on SNPs has minimal risk of inducing thrombosis

Scenario Continued

- Extensive advice on these topics is immediately sent electronically from the EHR to:
  - Her PHR
  - Her web portal page
  - Registries
- The patient asks about her risk of ovarian cancer as her aunt died from this disease
  - The physician queries the database
  - Her risk is found to be low based on:
    - The alleles she has inherited
    - Her exposure to epigenetic influences
  - The patient is reassured

Scenario Continued

- EHR stores data elements recording
  - History that genetic screening was performed with appropriate consent
  - Appropriate preventative treatment and counseling was provided
- This is reported as pay-for-performance data to payers and regulatory bodies as needed
- The EHR tracks whether or not she completes each recommended step based via community interoperability

Role of Electronic Health Records in Genomic Medicine

- Supplement research
  - Identify cohorts based on diseases, responses to care, SNP patterns, etc.
- Alerts and reminders
  - Inform clinician that a genetic test may be indicated
  - Identify patients at risk for certain diseases based on their genetic predisposition
    - Can be combined with risk factors (epigenetics)
  - Recommend therapies based on a patient's genome
    - E.g., Pharmacogenomic alerts

Evolving Role EHRs and Genomic Medicine

- EHR as an information resource
  - The amount of information on genetic disorders is overwhelming and growing rapidly
    - Consumer genomic screening tools on the rise
    - Clinicians will be asked to respond to this information provided by patients
  - EHR could narrow this to context specific information based on presentation
    - E.g., family history of tuberous sclerosis
  - Assist in providing counseling to patients

In Summary

- Genomics holds great promise for the future of medicine
- The EHR will play a central role in genomic related patient care, information management, and research
- Healthcare is not ready to absorb the information, costs and ethical issues tied to this rapidly expanding field

"The life sciences have entered a new era of research that will have a significant but as yet largely unpredictable impact on the way we see and shape our world, our health and our environment."

- *Netherlands Genomics Institute*

Questions?

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