Genetic Tests

• Genetic tests are often used for diagnosis for
  • Prenatal, pediatric and adult onset diseases
  • Diseases that run in families for unaffected but concerned individuals
Quest Diagnostics, a leading provider of medical tests, said prenatal and genetic mutation tests were one of the fastest-growing parts of its business
Possible Benefits from Genetic Tests

• Clinical
  – Avoidance of onset of disease
  – Curative treatment due to timely and accurate diagnosis
  – Avoidance of harms from inappropriate treatment or monitoring

• Psychological or social
  – Relief from uncertainty
  – Personal planning
  – Improved well-being
  – Fulfilment of patient wishes to be tested

• Public health
  – Decrease population morbidity and/or mortality from genetic disease
  – Decrease population frequency of treatment-related morbidity or mortality
Genetic Tests for Huntington Disease

• Huntington Disease
  – Incurable brain disorder that runs in families
  – Movement, cognitive, and psychiatric disorders
  – Disease onset around age 40
  – Dominant mutation in a gene on chromosome 4
    • Normal chromosomes – 35 repeats of CAG
    • Huntington disease mutation carriers – more than 35 repeats
  – If you have an affected parent, you have 50% chance of inheriting the disease mutation
  – Genetic tests available

• If you know Huntington disease runs in your family, would you be interested in taking the genetic test?

• What if you haven’t been tested but your children or parents want to get tested?
Genetic Test for Trisomy 18

• Trisomy 18
  – a genetic disorder in which a person has a third copy of material from chromosome 18
  – The extra genetic material affects normal development
  – Small head/jaws, low set ears, low birth weight, mental delay, muscle weakness
  – Half of infants with this condition do not survive beyond the first week of life. Some children have survived to the teenage years, but with serious medical and developmental problems.
  – Genetic tests are available during pregnancy

• Would you like to get tested during the pregnancy?
Genetic Test for Tay-Sachs Disease

• Tay-Sachs disease
  – a deadly disease of the nervous system passed down through families
  – the body lacks hexosaminidase A, a protein that helps break down a chemical found in nerve tissue called gangliosides. Without this protein, gangliosides build up in cells, especially nerve cells in the brain.
  – Symptoms usually appear when the child is 3 to 6 months old. The disease tends to get worse very quickly, and the child usually dies by age 4 or 5.
  – Recessive: When both parents carry the defective Tay-Sachs gene, a child has a 25% chance of developing the disease
  – most common among the Ashkenazi Jewish population
    • About 1 in every 27 members of the Ashkenazi Jewish population carries the Tay-Sachs gene

• Would you like to get tested for Tay-Sachs disease?

• Would the test results influence your decision on who to marry?
Prenatal Genetic Tests

• Down syndrome
  • Noninvasive or minimally invasive screening routinely done on pregnant women
    – Measure protein levels (PPAP-A and beta-HCG) in mother’s blood
    – Ultrasound imaging
  • Amniocentesis
    – More invasive tests done for women with increased risk based on less noninvasive procedure
      » Amniotic fluid contains leaked cells from fetus
      » Increases the chance of miscarriage
    – Also used for other chromosomal abnormalities, cystic fibrosis, sickle cell disease, Tay-Sachs disease
Cleft Lip & Palate

Six-month-old girl before going into surgery to have her unilateral complete cleft lip repaired

The same girl, 1 month after the surgery

The same girl, age 8, the scar almost gone
Genetic Tests for PKU

- Phenylketonuria (PKU)
  - A rare condition in which a baby is born without the ability to properly break down an amino acid called phenylalanine
  - Happens about 1 in 20,000 infants
  - Causes profound neurological and cognitive damage
  - Dietary intervention (limiting intake of phenylalanine) can make a major difference in the child’s health prospect
  - Genetic screening assay is a standard item for newborn screening panels
Prenatal Tests at Baylor College of Medicine

- ad-PEO 2 ANTI/SLC25A4
- ad-PEO 3 TWINKLE/PEO1
- Adenosine Deaminase Deficiency
- Angelman Syndrome UBE3A
- APECED AIRE
- Argininosuccinic Aciduria
- Argininosuccinic Aciduria ASL
- ARX Related Disorders
- BCS1L Related Complex III Deficiency BCS1L
- Carbamoyl Phosphate synthetase I Deficiency CPS1
- Cartilage Hair Hypoplasia RMRP
- CDKL5 Related Atypical Rett Syndrome CDKL5/STK9
- Charge Syndrome CHD7
- Citrin Deficiency SLC25A13
- Citrullinemia I ASS
- Cleidocranial Dysplasia RUNX2
- Coenzyme Q10 Deficiency COQ2
- Coenzyme Q10 Deficiency PDSS2
- COX10
- Cystic Fibrosis CFTR
- DGUOK (Deoxyguanosine Kinase)
- Diamond-Blackfan Anemia RPS19
- Fabry Disease GLA
- Familial Adenomatous Polyposis APC
- Fatal Infantile Lactic Acidosis w/mtDNA Depletion SUCLG1
- Focal Dermal Hypoplasia PORCN
- Fragile X Syndrome
- Guanidinoacetate Methyltransferase Deficiency GAMT
- Hereditary Fructose Intolerance ALDOB
- Huntington Disease
- Incontinentia Pigmentia
- L-Arginine:Glycine Amidinotransferase Deficiency GATM
- Lesch-Nyhan Disease HPRT1
- Leukoencephalopathy VWM EIF2B5
- Lowe Syndrome OCRL1
- MNGIE Syndrome (Thymidine Phosphorylase) TP
- MPV17
- Myotonic Dystrophy
- Nail-Patella Syndrome LMX1B
- Noonan Syndrome PTPN11
- X-linked Ichthyosis (STS Deficiency)
- Optic atrophy type 1 OPA1
- Ornithine Transcarbamylase (OTC) Deficiency OTC
- Osteogenesis Imperfecta, AR CRTAP
- Osteogenesis Imperfecta, AR LEPRE1
- Pelizaeus-Merzbacher PLP1
- POLG1 Related Disorders
- Purine Nucleoside Phosphorylase Deficiency
- Pyruvate Dehydrogenase Deficiency PDHA1
- Rett Syndrome MECP2
- RHD Molecular Typing
- Rothmund-Thomson Syndrome RECQL4
- SCO1
- SCO2
- SMCD COL10A1
- Spinocerebellar Ataxia 10 (SCA10)
- SURF1
- Thymidine Kinase TK2
- Wolman Disease
- X-linked Ocular Albinism GPR143
Medical Genetics Laboratories

The Medical Genetics Laboratories at Baylor College of Medicine have been dedicated to providing the medical genetics community with high quality comprehensive diagnostic services for over 30 years. By building on our institution's strengths in research and discovery, we aim to provide quality genetic testing services relevant to 21st century medicine.

Test Search

Search by disease, test name, test code, or keyword

#ABCDEFGHIJKLMNOPQRSTUVWXYZ
Prenatal Genetic Tests

• 450+ conditions including deafness, dwarfism and skin disease, can be diagnosed by testing fetal cells and this number is increasing.

• African-Americans are widely screened for sickle-cell anemia

• A panel that now includes nine tests for diseases common to Ashkenazi Jews has virtually eliminated the birth of children in the United States with Tay-Sachs
Ethical Issues for Prenatal Tests

• survivability of the child, quality of life of parents, quality of life of siblings, social needs.

• What defect, if any, is reason enough to end a pregnancy that was very much wanted?

• Cystic fibrosis: When both members of a couple among its patients in Northern California tested positive, 80 percent opted for the follow-up test of their fetus. Of those whose fetus was affected, 95 percent terminated the pregnancy. (Kaiser Permanente, NY Times)

• In vitro fertilization
Genetic Tests + Other Issues?

• Abortion: political/religious beliefs vs. personal feeling
  – How would you make decisions for yourself?
  – How would you advise your children?

• Results could be used for discrimination (e.g., employment or health insurance)

• Eugenics?
Genetic Tests for You vs Prenatal Tests?
Karyotyping

• Karyotyping
  – Taking dividing cells from the fetal sample and break them open on glass slides so that individual mitotic chromosomes spread out in a loose field
  – The slides are stained and photographed
  – Used for autosomal trisomies and sex chromosome anomalies
    • Turner (XO) syndrome
    • Klinefelter (XXY) syndrome
Biochemical Assays vs. Genetic Tests

• Genetic tests
  – directly genotype individuals’ DNA

• Biochemical Assays
  – Assay for biochemical product of the pathway in which disease genes are active
Biochemical Assays vs. Genetic Tests

• Genetic tests
  – Even if we determine the genotypes of individuals, we often cannot determine the effects of the mutations on phenotypes

• Biochemical Assays
  – When there are different mutations that influence the same biochemical pathway, a single assay for the pathway can determine a functional deficit
Biochemical Assays vs. Genetic Tests

• Why not biochemical assays? Advantages of genetic tests
  – Possible to detect the potential functional deficit before the symptoms (imbalance in the biochemical pathways) occur
    • Early intervention to reduce the damage from the disease
    • Can be critical for newborns
  – Non-invasive
    • Can be performed on cell sample from blood or from swabbing the inside of the cheek
    • Do not need the genes to be expressed
    • biochemical assays may involve invasive, difficult, and expensive procedure
Practical Challenges

• Interpreting the genetic tests result can be challenging for complex diseases
  • Individual patients may rely on false information on the web!
  • Reliable online resources such as GeneClinics, OMIM (Online Medelian Inheritance in Man) are becoming available
  • Consult medical geneticists or genetic counselors
  • Information on rare genetic disorders may be hard to find even at a clinic

• Developing cost-effective genetic tests
  – Development of genetic tests follows discovery of disease genes
  – Less incentives to develop genetic test for rare diseases
  – For newly discovered genes, genetic test may not be available
    • Patients can participate in research-based genetic testing
Genetic Tests for Complex Traits

• With whole-genome sequencing, in the future, genetic tests for complex traits will be available

• Challenges in interpreting test results for complex traits
  – Effect size of each mutation may be very small
  – The positive test results do not necessarily mean 100% certainty in developing the particular phenotype
    • Developing phenotypes only under “certain” conditions that are difficult but not impossible to avoid
  • How to interpret the “maybe” results?
Genetic Tests for Breast Cancer

- BRCA1 and BRCA2 testing
  - 36-85% chance of developing breast cancer for BRCA-positive women
    - 13% chance for the general population
  - Possible risk-reducing strategies for BRCA-positive women
    - Increased surveillance for early detection
    - Risk-reduction surgery to remove part of breast and ovarian tissues
    - Changing life style
  - But the test results are not definitive answers to whether you’ll develop breast cancer!
Social Ethical Issues

• Genetic screening for non-disease phenotypes such as cosmetic traits, IQs
  – How do we interpret the result?
  – How do we make use of the result?
Other Types of Genetic Tests

• Pharmacogenomic testing
  – Patients requiring specific medicines might undergo a genetic test to
determine the likely rate of drug metabolism, thus providing the
doctor with critical information for proper dosage
  – E.g., Cytochrome P450 (CYP450) tests
    • Our body contains many P450 enzymes to process drug
    • Genetic variation in these enzymes can affect how each person
      responds to the drug

• Identification of individuals
  – Paternity test, identifying relatives
  – Law enforcement – identifying criminals
Policy for Quality Control for Lab Tests

• Clinical Laboratory Improvement Amendments (CLIA)
  – Sets the standard for lab testing quality
  – Established in 1988
  – The objective of the CLIA program is to ensure quality laboratory testing. Although all clinical laboratories must be properly certified to receive Medicare or Medicaid payments

Policy for Quality Control for Lab Tests

- Clinical Laboratory Improvement Amendments (CLIA)
  - The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). In total, CLIA covers approximately 244,000 laboratory entities.

  - Applies to all tests on "materials derived from the human body for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings"

Genetic Counseling

• Medical geneticists
  – MD training with subspecialty in medical genetics
  – Often specialty training in pediatrics or internal medicine
  – With whole-genome sequencing, the process for diagnosis is increasingly more complicated
    • Gene-gene interaction
    • Gene-environment interaction

• Genetic counselors
  – Trained in Master’s program and board-certified
  – Works with medical geneticists to offer counseling to patients
Genetic Counseling

• Genetic counseling
  – explains the nature, usefulness and risks associated with genetic tests
  – assures that participation in genetic testing is autonomous, or based on participants’ understanding of the relevant information

• Genetic counselors
  – identify families at risk of genetic conditions
  – investigate the genetic condition that is present in the family
  – interpret information about the disorder
  – analyze inheritance patterns and risks of recurrence
  – with the family, review the options that are available
  – Pre- and post-test counseling
23andMe: Policy/Legal Issues

• Does the test provide scientific information or medical information?

• Direct-to-consumer model: genetic test results are available directly to consumers without going through medical professionals or genetic counseling
Policy/Legal Issues

- Health-related genetic tests were suspended by FDA, beginning November 2013
  

- Only genome-based ancestry service is provided now

- 23andMe is working with FDA for a resolution
  
  
Summary

• Genetic tests have been used mainly for prenatal screening but will be more widely used for adult-onset diseases in the future

• Genetic counselor and medical geneticists can assist patients for interpreting the results from genetic tests

• Issues involved in interpreting the test results
  – Ethical issues – what actions to take given the test results
  – Challenges in interpreting results for complex traits