Conflict of Interest

• Neither I nor any member of my immediate family has a financial relationship or interest with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device.
Learning Objectives

Upon completion of this session, you will be able to

- Describe the utility of genetic testing, including karyotype analysis, FISH, chromosomal microarray analysis, molecular testing and biochemical testing
- Discuss the major clinical features of selected genetic syndromes, associations, or sequences
- Discuss the teratogenic effects of fetal alcohol syndrome
## Genetic Testing

<table>
<thead>
<tr>
<th>Name</th>
<th>Test</th>
<th>Abnormalities Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>Microscopic evaluation of all chromosomes</td>
<td>Trisomies, large rearrangements, and inversions</td>
</tr>
<tr>
<td></td>
<td>Resolution: 1-10 Mb</td>
<td></td>
</tr>
<tr>
<td>Flurecence <em>in situ</em> hybridization (FISH)</td>
<td>Single chromosome locus Resolution: Submicroscopic changes (about 1 Mb)</td>
<td>Continuous gene deletions/duplications (copy number variants)</td>
</tr>
<tr>
<td>Chromosomal microarray analysis (CMA)</td>
<td>≥ 180K oligonucleotides or millions of single nucleotide polymorphisms (SNP) throughout genome</td>
<td>Oligonucleotide or SNP duplications/deletions (copy number variants)</td>
</tr>
<tr>
<td>Molecular testing (Sanger sequencing or whole exome sequencing)</td>
<td>Sequencing of exons and exon/intron borders of specific gene(s)</td>
<td>Point mutations, frameshifts, small deletions, trinucleotide repeats</td>
</tr>
<tr>
<td>Biochemical testing</td>
<td>Metabolites associated with metabolic disease</td>
<td>Amino acids, organic acids, ammonium, acylcarnitine profile, etc.</td>
</tr>
</tbody>
</table>
Genetic Syndromes & Teratogens

• HIPAA and copyright guidelines limit use of pictures in handouts
• Pictures do not reproduce well in handouts
• Handout does not include most pictures
• Google Images is a good resource for representative images of syndromes
Trisomy 13

- Associated with AMA
- Microcephaly
- Microophthalmia
- Heart malformations
- Ear anomalies
- Severe growth and developmental impairment
- Cutis aplasia
- Holoprosencephaly
- Orofacial clefting
- Polydactyly (postaxial)
- 45% die in first month, 85% in first year
Trisomy 18

- Associated with AMA
- Microcephaly
- Microophthalmia
- Heart malformations
- Ear anomalies
- Severe growth and developmental impairment
- Prominent occiput
- Micrognathia
- Overlapping fingers
- Hypoplastic nails
- Clubfoot
- Seizures
- 50% die in first week, 95% in first yr
Klinefelter Syndrome

- 80%: XXY
- Remainder mosaic or variable sex chromosome number (eg. XYY, XXY, XXXY)
- Average or above average adult height
- 50% with delayed speech
- Average IQ with mild learning disability
- 30% with delayed emotional development
- Adults may have behavior problems
Klinefelter Syndrome

- Hypergonadotrophic hypogonadism
- Most are sterile
- Accounts for 5-15% of sterility in males
- Sparse facial hair
- Gynecomastia
- Increased risk of carcinoma of breast and mediastinal tumors
- 20% with major malformations (no pattern of anomalies)
- Treat with androgen replacement
Turner Syndrome

- 1/ 4,000 newborns
- Causes:
  - 50%: 45,X
  - 25%: RingX or isoX
  - 25%: Mosaic (45,X/46,XX or XY)
- Short, broad, webbed neck
- Broad chest, widely spaced nipples
- May only cause growth restriction
- Gonadal dysgenesis common
- May have hypothyroidism
- Ovarian hormone replacement required
- Growth hormone may be provided
Turner Syndrome

- Heart anomalies (coarctation)
- Can have renal anomalies
- Autoimmune disease more common (diabetes, IBD)
- IQ is normal, but may have cognitive impairment
  - Delayed speech
  - LD
  - Visual-spatial problems
Additional Sex Chromosome Syndromes

• 47, XYY
  – 1/1000 newborn males
  – Tall stature
  – 1/3 with language delay; lower than normal IQ
  – Increased risk of criminal behavior
  – Normal gonadal development

• 47, XXX
  – 1/1200 newborn females
  – No major dysmorphic features
  – Language delays and below normal IQ
  – Fertility ranges from normal to complete infertility with streak gonads
Velocardiofacial Syndrome

- 22q11 deletion
- Example of contiguous gene deletion syndrome
- 1 in 2,000-4,000
- Cleft palate
- Heart defects
- Characteristic facial features
- Immune dysfunction
- Learning disability
- Mental disease in 20%
- Typically de novo deletion
Prader-Willi

- Feeding problems in infancy, then hyperphagia and obesity
- Small hands and feet
- Hypogonadism
- Intellectual disability

Angelman

- May also have feeding problems
- Distinctive facial appearance
- Early speech delay
- Intellectual disability
- Seizures, spasticity
- Laughter outbursts
Genetics of PWS and AS

- Abnormality of 15q11-q13
  - Methylation testing
    - Deletion
    - Uniparental disomy
    - Imprinting center mutation
  - Point mutation in UBE3A (Angelman only)
- Phenotype depends on parental origin of abnormal chromosome
  - PWS: Deletion or abnormal imprint of paternal region of 15q11
  - AS: Deletion or abnormal imprint of maternal region 15q11
Beckwith-Wiedemann syndrome

• Overgrowth syndrome
  – Macrosomia, macroglossia
  – Hemihyperplasia
  – Visceromegaly
• Ear creases/pits
• Omphalocele
• Renal anomalies
• Neonatal hypoglycemia
• Embryonal tumors
  – Wilms, hepatoblastoma, neuroblastoma, rhabdomyosarcoma
  – AFP every 6 weeks, abd U/S every 3 months until 8yo
• Genetics: *CDKN1C* mutation, 11p15 methylation abnormality
Neurofibromatosis Type I

- Autosomal dominant
- NIH Criteria (2 or more)
  - $\geq 6$ café au lait macules
    - $>5$mm in prepubertal
    - $>15$ mm in postpubertal
  - $>2$ neurofibromas or
    - $>1$ plexiform neurofibroma
  - Axillary freckling
  - $\geq 2$ Lisch nodules
  - Tibial pseudoarthrosis
  - Optic glioma
  - Family history

Photos from GeneTests.org
Neurofibromatosis Type I

- Café au lait macules can increase in number during first few years of life
- Optic gliomas typically develop in first 6 years of life
- 50% with learning disability
- Progressive scoliosis usually only seen at 6-10 years of age
- Hypertension is common in adults
- Malignant peripheral nerve sheath tumors in 10%
- Increased risk for cerebral vasculopathy
- Somewhat increased risk for leukemia and other tumors (GI tumors)
Tuberous Sclerosis

• Autosomal dominant
• Mutation in \(TSC1\) or \(TSC2\)
• Skin
  – Facial angiofibromas
  – Hypomelanotic macule
  – Shagreen patch
  – Ungual fibromas
Tuberous Sclerosis

- **Brain**
  - Cortical dysplasias
  - Subependymal nodules
  - Subependymal giant cell astrocytomomas (SEGAs)
  - Epilepsy, autism, ADHD, LD, ID
- **Kidney:** angiomyolipomas, cysts, renal cell carcinoma
- **Heart:** rhabdomyomas, dysrhythmias
- **Lungs:** lymphangioleiomyomatosis (LAM) in women
- **Increased risk for neuroendocrine tumors**
Ehlers-Danlos

- Autosomal dominant
- Heterogeneous group of connective tissue disorders
- Classic type (Type I)
  - Skin hyperextensibility
  - Atrophic scars
  - Joint hypermobility
  - Smooth, velvety skin
  - Easy bruising
  - Hernia, rectal prolapse
Ehlers-Danlos Type IV

- Vascular type
  - Autosomal dominant
  - Mutation in COL3A1
  - Arterial, intestinal or uterine rupture
  - Translucent skin
  - Joint hypermobility with subluxations
  - Easy bruising
Marfan Syndrome

• Autosomal dominant
• Mutation in *Fibrillin-1*

• Diagnostic criteria (> 2)
  – Family history
  – Skeletal system
  – Ocular system
  – Cardiovascular
  – Lumbosacral dural ectasia
  – Pulmonary (minor criteria)
    • Pneumothorax
    • Apical blebs
Marfan Syndrome

- Skeletal system
  - Arachnodactyly
  - Pectus carinatum or excavatum
  - Wrist and thumb signs
  - Typical facial features
  - Pes planus
- Ocular system
  - Ectopia lentis
  - Miosis
- Cardiovascular
  - Progressive aortic root dilatation
  - Treat with beta-blocker
Osteogenesis Imperfecta

- “Brittle bone disease”
- Autosomal dominant
- Mutations in COL1A1 or COL1A2 cause defect in a major structural protein of bone and fibrous tissue
- Bone fragility leads to fractures
- Progressive bone deformities
- Short stature
- Blue sclera
- Poor dentition
- Hearing impairment
- Spectrum of severity (Types I-IV)
- In differential diagnosis for NAT
Achondroplasia

• Autosomal dominant
• Mutation in FGFR3
  – 98%: G to A at 1138
  – 2%: G to C at 1138
• Glycine to arginine at codon 380
• Rhizomelic short stature
• Enlarged head
• Flat nasal bridge
Achondroplasia

- Short fingers and trident hand
- Short vertebral bodies
- Interpediculate distance narrowing in lumbar spine
- Anterior wedging of vertebrae – kyphosis
- Normal cognition
- Delayed motor development
- Increased rate of sudden death in infancy and early childhood
- Narrow spinal cord can cause compression
- Otitis media and hearing loss
Bardet-Biedl

- Autosomal recessive (may be oligogenic)
- Truncal obesity
- Rod-cone dystrophy (night, then legal, blindness)
- Postaxial polydactyly
- Hypogonadism (males)
- Genital abnormalities (females)
- Renal abnormalities lead to ESRD
- Global developmental delay, learning disability, ataxia
- Anosmia
CHARGE Syndrome

- Autosomal dominant
- 60-70% with mutations in CHD7
- Coloboma
- Heart defect
- Atresia choanae
- Retarded growth/development
- (Cranial neuropathies)
- Genital anomalies/hypogonadism
- Ear anomalies/deaf
CHARGE Syndrome

• Other associated features
  – Developmental delays and hypotonia
  – May have behavior problems
  – Feeding difficulties
  – Growth deficiency (70-80%)
  – Orofacial clefts (15-20%)
  – Tracheoesophageal fistula (15-20%)
  – Other life-threatening conditions in infancy
Treacher Collins Syndrome

- Mandibulofacial dysostosis
- *Treacle* or *TCOF1*
- Downslanting palpebral fissures with coloboma of outer third of lower lid
- Malformed pinnae and middle ear malformations
- Nose appears large due to malar and supraorbital ridge hypoplasia
- Cleft palate, rarely CL/P
Apert/Crouzon

- Mutation in *FGFR2*
- Coronal craniosynostosis
- Flat faces
- Midface hypoplasia
- Proptosis
- Hearing loss
- Syndactyly
- Heart anomalies
- Variable IQ
Fragile X Phenotype

Somatic features (prepubertal % - postpubertal %)
- Prominent ears (78-66%)
- Long face (64-80%)
- Macroorchidism (54-92%)
- High-arched palate (51-63%)
- Hyperextensible joints (81-49%)
- Flat feet (82-60%)
- Heart murmur or click (16-29%)

Neurologic features
- Moderate to severe ID (high variability)
- IQ decline
- Autistic features
- Ataxia
- Hyperactivity
- Aggression

(Photos from www.FRAGILEX.org)
Fragile X Phenotype

- Females usually less affected than males due to X-inactivation
- Phenotype depends on the number of cells that contain normal X as active chromosome (activation ratio)
- Phenotype ranges from normal to severely affected
- Severity of intellectual disability correlates with prominence of dysmorphic features

Fragile X testing is indicated for girls with GDD/ID

(Photos from www.FRAGILEX.org)
Trinucleotide Repeats: Fragile X

FMR1 gene sequence

| Normal | acagtgcaatgatac $\text{(CGG)}_{N=5-44}$ | agagtctcagactacg |
| Mutable | acagtgcaatgatac $\text{(CGG)}_{N=56-200}$ | agagtctcagactacg |
| Full mutation | acagtgcaatgatac $\text{(CGG)}_{N>200}$ | agagtctcagactacg |

Dynamic mutation
FMR1- Related Phenotypes

Onset in adulthood
tremor and ataxia
(85 CGG repeats)

Premature ovarian failure
(91 CGG repeats)

Intellectual disability, autism,
characteristic facial features
(450 CGG repeats)
Muscular Dystrophies
Duchenne and Becker

- Childhood onset of progressive myopathy
- X-linked (mutations in dystrophin gene)
- Cognitive impairment is not rare
- Pseudohypertrophy and Gowers sign
- Massively elevated CPK (diagnostic)
- Genetic testing available
- Treatment
  - Physical therapy and nutrition
  - Steroids seem to improve strength and maintain ambulation
- Prognosis death/ventilator dependence by adulthood for Duchenne, survival into adulthood for Becker type.
Rett Syndrome

- Neurodegenerative disease in girls
- Mutations in MECP2 on X chromosome
- 1-3/10,000 live births
- Acquired microcephaly
- GDD, then regression
- Autistic-like behavior
- Seizures, ataxia, hyperventilation episodes
- Stereotypic hand movements

(From website RettSyndrome@groups.msn.com)
VACTERL Association

- Cause is usually unknown (not a syndrome)
- Diagnostic criteria - 3/7 following features:
  - **V**ertebral anomalies
  - **A**nal atresia
  - **C**ardiac anomalies (TOF, transposition, VSD)
  - **T**racheo**E**sophageal fistula or esophageal atresia
  - **R**enal anomalies (aplasia, hydronephrosis)
  - **L**imb anomalies (radial ray anomalies, polydactyly, syndactyly, triphalangeal thumb)
  - Growth deficiency
  - Tethered cord, occipital encephlocele
  - Increased incidence in infants of diabetic mothers
Sturge-Weber Syndrome

• Facial cutaneous hemangioma (port wine stain) in ophthalmic division of trigeminal nerve
• Angiomas of pia
• Refractory focal seizures, developmental delay, and hemiparesis/hemianopsia
• Sporadic
• HCT: subcortical tram-track calcifications
• Brain MRI: leptomeningeal enhancement
Robin Sequence

Mandibular hypoplasia

Posterior tongue displacement

Cleft palate
Potter Sequence

- Bilateral renal dysgenesis, polycystic kidneys, urinary tract obstruction, etc

  ↓

- Oligohydramnios

  ↓

- Compression deformity of face and limbs, arthrogryposis, growth restriction, lung hypoplasia

  ↓

- Growth can be monitored by serial ultrasounds
Amniotic Bands

- Disruption
- Extrinsic amniotic band destroys tissue
- Range of severity
  - Ring constriction
  - Syndactyly
  - Talipes equinovarus
  - Craniofacial disruptions and clefts
  - Amputations
  - Body wall defects
- Almost always sporadic
Teratology

- Adverse effects of environmental toxin (teratogens) on growth and development of embryo
- Drugs, infection, radiation, maternal disease
- Time of exposure is usually important (except for alcohol)
  - Critical time is 14-60 days
  - Effect can differ based on timing
- Recognizable pattern of abnormalities
- Threshold and dose-response
- Species-specific
- Pathogenesis largely unknown
Fetal Alcohol Syndrome

- In utero alcohol exposure
- 1/30 women abuse alcohol
- 6% of their children have FAS
- Mild to moderate microcephaly
- Dysmorphic face
- Heart defects
- Pre- and postnatal growth restriction
- CNS malformations
- Intellectual disability and learning disorders
- Behavior problems
References

• Gene Reviews: www.genetests.org
• Gorlin’s Syndromes of the Head and Neck, 2nd Edition
• Online Mendelian Inheritance in Man
• Smith’s Recognizable Patterns of Human Malformations, 6th Edition
• Thompson and Thompson’s Genetics in Medicine, 6th Edition
Change in Practice Opportunities

• Review the key features of common genetic syndromes
• Confirm all patients with intellectual disability have a chromosomal microarray analysis and Fragile X testing
• Correlate specific genetic conditions with the genetic testing that would be performed to diagnose conditions
• Utilize genetic references to help diagnose genetic conditions