Value of A Genetic Work-Up and Reasons for Referral

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Disclosures

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation
Objectives

• At the end of this presentation I hope you all will:
  – Understand the value of a genetic work-up
  – Be able to identify reasons for referral to a geneticist
  – Be able to employ some strategies to approach parents about a potential genetic referral
  – Be able to identify tools and resources to assist in the referral process
Overview

- Medical Benefits
- Financial Benefits
- Family Planning Information
- Neonatal Referrals
- Neonate, Infant, Child Referrals
- Childhood Referrals
- Talking to Parents About a Genetic Referral
- Tools and Resources
Goals for Change

• Patients with a significant family history or medical concern raised on exam suggestive of a genetic condition have a documented follow-up plan of care and indication that this was discussed with the family

• Practices have a tracking system in place for genetic referrals

• Patients with identified genetic conditions (i.e. registry patients) have genetic services offered, at least initially and have documented next steps and follow-up as appropriate
Medical Benefits

• Having a confirmed genetic diagnosis can:
  – Highlight potential complications
  – Guide diagnostic studies or surveillance strategies
  – Provide important prognostic information
  – Guide EIP or IEP services and assist the Child Study Team
Case #1
Cytogenetic Diagnosis and Surveillance

• Newborn male referred because of a ventricular septal defect (chromosomes normal)
• At surgery thymic hypoplasia was noted, genetics was consulted, and FISH testing for a 22q deletion was performed
• This test was positive and dad was evaluated and found to also carry this deletion
Case #1

Follow-Up and Surveillance

• Child evaluated for hypocalcemia (this was identified) and he was placed on a synthetic vitamin D analog to increase calcium levels

• He was enrolled in an early intervention program and received services prior to enrollment in a preschool handicapped program

• He was evaluated for T-cell deficiency and provided prophylactic antibiotics
Case #2
Cytogenetic Diagnosis and Surveillance

• Infant referred for dysmorphic facial features
• Chromosome analysis was performed and demonstrated extra-genetic material on chromosome 22
• Child was referred for renal sonogram and echocardiogram despite no cardiac murmur
• He was eventually found to have a single kidney and total anomalous pulmonary venous return that required immediate surgery
Case #3
Cytogenetic Diagnosis and Surveillance

• 5 ½ year old girl referred for speech delays and streaky hyperpigmentation of the skin
• Child is in a regular kindergarten class and receiving speech therapy twice a week
• Teacher feels she is not trying very hard and needs to be more motivated with handwriting
• Chromosome analysis demonstrates a mosaic marker chromosome (isodic 9p) = two extra copies of 9p
Case #3
Conclusions
• This chromosomal change is likely associated with more significant learning issues (noted hypotonia and weak hands)
• Echocardiogram and renal ultrasound are recommended
• School placement should be re-evaluated and service provision increased to include OT/PT
• Risks for recurrence are very small for parents
Case #4
Neurofibromatosis Type 1

- A 2 ½ year old boy is referred for 6 café-au-lait spots, but no other features of NF
- Neurodevelopmental assessment is normal
- He is also referred for a dilated eye exam by a pediatric ophthalmologist
- Exam is significant for pallor of the left optic nerve
- Subsequent MRI demonstrates a left optic nerve glioma
Case #4
Conclusions

• Close follow-up of the vision in the left eye over 6 months shows decreasing visual acuity.

• He is referred for chemotherapy for the optic nerve glioma (ONG) and has a wonderful response to treatment with shrinkage of the ONG and return of vision on the left.

• He is followed yearly by the multidisciplinary NF team and monitored for complications of NF1.
Case #5
Disaster Avoidance

• 12 year old boy from Puerto Rico with albinism is referred for genetic evaluation and counseling because his mom is pregnant
• He has typical features of albinism with nystagmus and poor visual acuity, blonde/red hair and fair skin with some freckles
• He is asked about easy bruising and his mom and he report that he does in fact bruise quite easily
Case #5

Conclusion

• Based on this “tip” we suspect that he has Hermansky-Pudlak syndrome instead of simple albinism (even though both are autosomal recessive conditions)

• He is at risk for excessive bleeding with minor and major surgical procedures, pulmonary fibrosis and granulomatous colitis

• Knowing this we can better prepare for surgeries in the future (DDAVP and hematology evaluation), no aspirin, close pulmonary follow-up (no smoking!!) and monitor for GI symptoms
Financial Benefits

• As physicians we also have a moral obligation to utilize medical resources appropriately

• For many patients referred for genetic evaluation, they have already seen 3 to 6 other subspecialists before landing in our office

• They have also undergone extensive, expensive and often unnecessary testing
Cases #1 and #2
Unnecessary Testing

• A 1 year old girl comes in for evaluation for neurofibromatosis. She has a head circumference just above the 95th percentile and has just undergone a brain MRI for “macrocephaly” and to rule out optic nerve gliomas

• A 15 year old boy comes in for routine neurofibromatosis care and has been followed previously by a pediatric neurologist, with annual MRIs beginning at the age of 3 years
Case #3
The Medical Odyssey

• A 4 year old child with autism has been evaluated and followed by his pediatrician and developmental pediatrician since his diagnosis at the age of 2 years

• He has been seen by a dermatologist for vitiligo, a neurologist for hypotonia, and a nephrologist for a kidney cyst detected incidentally on a scan after a urinary tract infection

• Summertime exam demonstrates several well-demarcated hypopigmented macules and the diagnosis is...tuberous sclerosis
Family Planning Information

• Couples with a child who may have a genetic condition are often concerned about risks for recurrence
• Knowing the genetic diagnosis can more clearly define these risks and help them make rational family planning decisions
• More and more options for couples are now available
Case #1
Pregnant Family Member

• A woman is referred for genetic counseling because her sister is pregnant and she has two children with severe intellectual disabilities and minor birth defects

• The family history is otherwise unremarkable and prior genetic testing including chromosome analysis on the brother and sister were normal/negative

• A CGH microarray is ordered on the daughter for completeness’ sake
Case #1 Pedigree (A)
Case #1 Pedigree (B)
Case #1 Conclusion

• Pregnant sister is actually at risk of being a translocation carrier and could also have an affected child

• Immediate specialized cytogenetic studies should be offered to her to assess her risks and determine if prenatal testing is indicated
Case #2
Reassurance After Testing

• A 40 year old woman is referred because of a family history of an X-linked condition in her two maternal half-brothers and maternal uncle

• They have bilateral congenital sensorineural hearing loss, a progressive peripheral neuropathy and later onset optic nerve atrophy possibly caused by a mutation in the CMTX5 gene

• Molecular testing on one of her half-brothers identifies a CMTX5 mutation
Case #2 Pedigree (A)
Case #2 Pedigree (B)
Case #3
Preimplantation Genetic Diagnosis

- 10 month old referred for borderline microcephaly
- Exam is significant only for a head circumference at the 5\textsuperscript{th} percentile for age and 2-3 toe syndactyly
- Chromosome testing and a 7 dehydrocholesterol analysis are sent and the latter is positive
- Diagnosis is Smith-Lemli-Opitz syndrome
Case #3 Conclusion

- We initiated a high cholesterol diet for the boy which improved his weight gain and disposition.
- Mom discovered she was very early in her second pregnancy and we were able to do genetic testing to identify the gene mutations and test the fetus.
- Mom was able to use this information in her third pregnancy to prevent having another affected child through preimplantation genetic diagnosis.
## Neonatal Referrals

### Finding
- Abnormal newborn screening test
- Congenital hypotonia or hypertonia
- Unexplained intrauterine growth retardation (IUGR)

### Why to Consider
- R/O inborn error of metabolism
- R/O chromosomal, metabolic or syndromic dx
- R/O chromosomal, metabolic or syndromic dx
### Neonate, Infant or Child (1)\(^1\)

#### Finding
- Single major or multiple minor anomalies
- Dysmorphic feature that are not familial +/- dev delays
- Known metabolic condition or symptoms of a metabolic disorder
- Abnormal brain MRI findings - malformation, leukodystrophy, periventricular calcifications

#### Why to Consider
- R/O chromosomal or syndromic dx + recur risks
- R/O chromosomal or syndromic dx
- Diagnose the disorder, initiate treatment and management + recur risks
- R/O chromosomal or syndromic dx
# Neonate, Infant or Child (2)

## Finding

- Unusual growth pattern – overgrowth, short stature, hemihypertrophy
- Possible connective tissue disorder – joint laxity, poor healing, marfanoid habitus
- Congenital eye defect
- Significant deafness or hearing loss not secondary to recurrent otitis medias

## Why to Consider

- R/O chromosomal or syndromic dx – BWS, Turner syndrome, Sotos syndrome
- R/O Ehlers-Danlos, Marfan syndrome etc...
- R/O syndromic dx
- R/O syndromic or non-syndromic form of hearing loss
# Neonate, Infant or Child (3)¹

## Finding
- Cardiomyopathy not secondary to viral infection
- Six or more café-au-lait spots greater than 0.5 cm
- Unusual skin findings or multiple types of lesions
- A parent with a known chromosomal abnormality or rearrangement (especially if dysmorphic or delayed)

## Why to Consider
- R/O mitochondrial or metabolic condition or synd
- R/O neurofibromatosis (NF) type 1
- R/O chromosomal or syndromic dx
- R/O chromosomal abnormality
Neonate, Infant or Child (4)\(^1\)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Why to Consider</th>
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<tr>
<td>• Bilateral or multifocal malignancies (Wilms or retinoblastoma)</td>
<td>• R/O cancer syndrome or other chromosomal or syndromic dx</td>
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<tr>
<td>• Clotting disorder such as hemophilia or thrombosis</td>
<td>• R/O inherited clotting disorder</td>
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<tr>
<td>• Suspected chromosomal or syndromic dx</td>
<td>• Dx confirmation, prognosis, management + recur risk</td>
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<tr>
<td>• Significant family hx of medical or psychiatric problem that may affect</td>
<td>• Counseling for dx, diagnostic testing, inheritance and risk assessment</td>
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<td>your patient</td>
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## Child Referrals

### Finding
- Unexplained intellectual disabilities or dev delays
- Autism or pervasive developmental disorder
- Unusual behaviors, esp when seen with dev delays
- Progressive muscle weakness
- Other neurologic condition with genetic implications

### Why to Consider
- R/O chromosomal, syndromic or metabolic dx
- R/O chromosomal or syndromic dx
- R/O chromosomal or syndromic dx
- Confirm suspected muscle or nerve diagnosis
- R/O genetic diagnosis
## Change Package

<table>
<thead>
<tr>
<th>Key Change</th>
<th>Ideas and Tools for Change</th>
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| 2. Identify and Follow-Up with Patients Identified at Risk through Family History or Clinical Evaluation | **At-risk patient is defined as a patient with a positive family history and/or identified clinical concerns (physical signs, cognitive concerns) of a genetic condition.**
- Develop and implement a follow-up plan for patients with a potentially at-risk family history or signs of a genetic condition.
  - Identify patients with a positive family history or signs of a genetic condition.
  - Review the article, “Genetic red flags: clues to thinking genetically in primary care practice”.
  - When collecting family history information, ask related follow-up questions as appropriate. Utilize the following example follow-up questions that correspond with the family history tool that is utilized.
    - Family History Checklist follow-up questions.
    - Pediatric Genetic Screening Questionnaire follow-up questions.
  - Review the “Criteria for Consideration of a Genetic Referral” document.
  - Review the “Ethnic Predispositions” Document.
  - Prepare to communicate the identification of an at-risk family history or genetic condition with patients and families. Review strategies and scripts to assist clinicians with discussions for at-risk family history.
  - Track, follow-up, and document all results and activities for these patients. Communicate results and their implications to patients and families. Document the follow-up plan in patient’s chart and document that the follow-up/plan of care was discussed with the patient/family.
  - Utilize a referral tracking mechanism to follow through with your patient. |
Indications for Possible Referral for Genetic Evaluation

The purpose of this tool is to provide primary care practitioners with an at-a-glance view of medical conditions/concerns that commonly prompt referrals to a geneticist. It is not intended as a list of conditions/concerns for which you must refer, but is a guide for your consideration.

Significant neurological problems

- Developmental delay/intellectual disability
- Autism spectrum disorder
- Significant hypotonia, hypertonia, and/or spasticity
- Progressive muscle weakness/peripheral neuropathy/ataxia
- Seizure disorder (especially hard to control)
- Brain malformation/abnormal brain MRI findings
- Congenital deafness

Congenital anomaly

- Congenital heart disease
- Congenital diaphragmatic hernia
- Renal agenesis
- T-E fistula
- Limb or bone malformation such as clubfoot, missing or extra digits
- Dysmorphic features

Growth problems

- Intrauterine growth restriction/small for gestational age
- Failure to thrive
- Short stature
  - Disproportionate growth/hermihypoplasia/mastoid habitus
- Microcephaly or macrocephaly

Miscellaneous

- Abnormal skin findings – café-au-lait spots, multiple lipomas, ash-leaf spots
- Cardiomyopathy not due to viral infection
- Clotting abnormalities – thrombophilia or excessive bleeding
- Bilateral or multifocal malignancies such as Wilms tumor or retinoblastoma

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Talking to Parents about a Genetic Referral

- Dealing with reticent or anxious parents
  - “On my exam today I see _X finding_. I want to be sure there isn’t a genetic connection and, in order to be thorough, I am recommending that we seek the advice of a geneticist.” BAP
  - “_Jonny/Joanie_ has been diagnosed with _[(learning disorder/autism/developmental delays)]_ and I would like to see if we can identify a possible cause for these difficulties. Therefore I am suggesting that _Jonny/Joanie_ be seen by a geneticist.” BAP
  - “In order to address your question, I would like to refer to Medical Genetics.” JM (John Moeschler)
  - “In order to best care for your child, I would like Medical Genetics to help me with the following question: ____________________?” JM
  - “I understand you are not concerned, but in order to provide best care, I need __________ from Medical Genetics.” JM
Tools and Resources

• AAP Committee on Genetics Health Supervision Guidelines - www.aap.org/visit/cmte18.htm
• eMedicine – http://emedicine.medscape.com/pediatrics_genetics
• ACMG Newborn Screening ACT Sheets – www.acmg.net/resources/policies/ACT/condition-analyte-links.htm
• Genetic Alliance – http://geneticalliance.org
• Unique rare chromosome group – www.rarechromo.org
• Genetics and rare conditions – www.kumc.edu/gec/support
• National Organization of Rare Disorders – www.rarediseases.org
• NY Online Access to Health – www.noah-health.org
Bibliography


Goals for Change
“Call to Action”

• Patients with a significant family history or medical concern raised on exam suggestive of a genetic condition have a documented follow-up plan of care and indication that this was discussed with the family

• Practices have a tracking system in place for genetic referrals

• Patients with identified genetic conditions (i.e. registry patients) have genetic services offered, at least initially and have documented next steps and follow-up as appropriate
## Breakout Session A and B

**10:00 – 10:45 am**

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<thead>
<tr>
<th>Breakout Session A</th>
<th>Breakout Session B</th>
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<tr>
<td><strong>Topic:</strong> Connecting with Others in the Medical Neighborhood</td>
<td><strong>Topic:</strong> Communicating with Families about Family History and Genetics</td>
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<tr>
<td><strong>Speakers:</strong> Amy Driscoll, Ruth Gubernick</td>
<td><strong>Speakers:</strong> Abe Elias, Ingrid Larson</td>
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<td><strong>Location:</strong> Conference Room 1F</td>
<td><strong>Location:</strong> Board Room</td>
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After the break, choose a Breakout Session to attend. Teams should consider splitting up so your team has representation at each session.