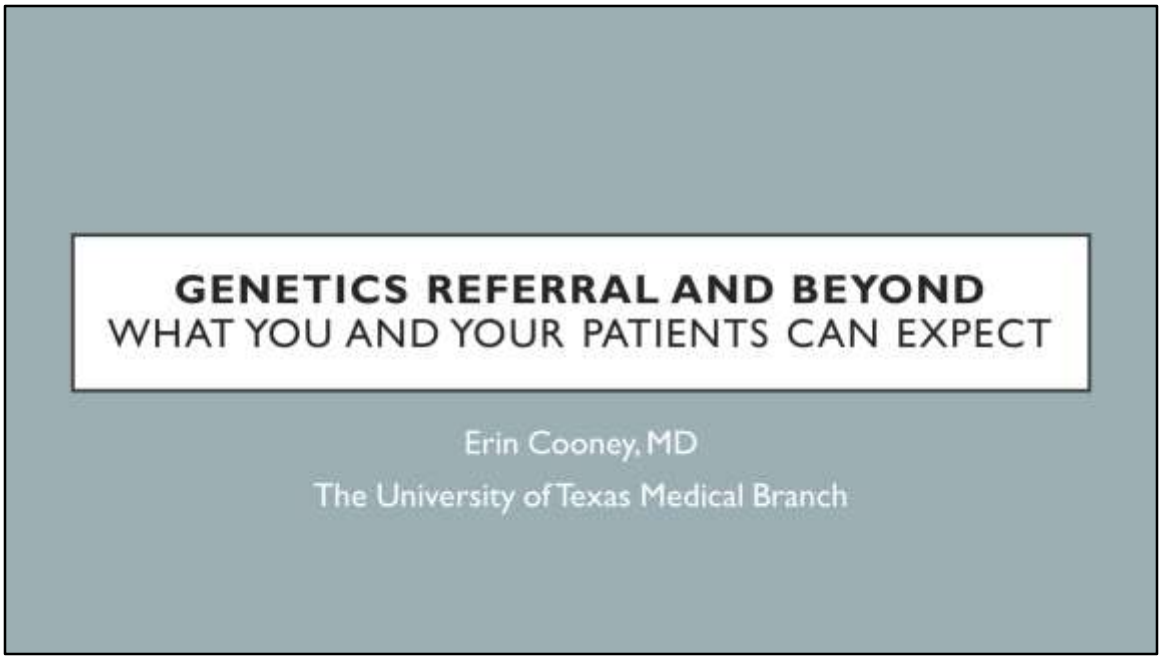
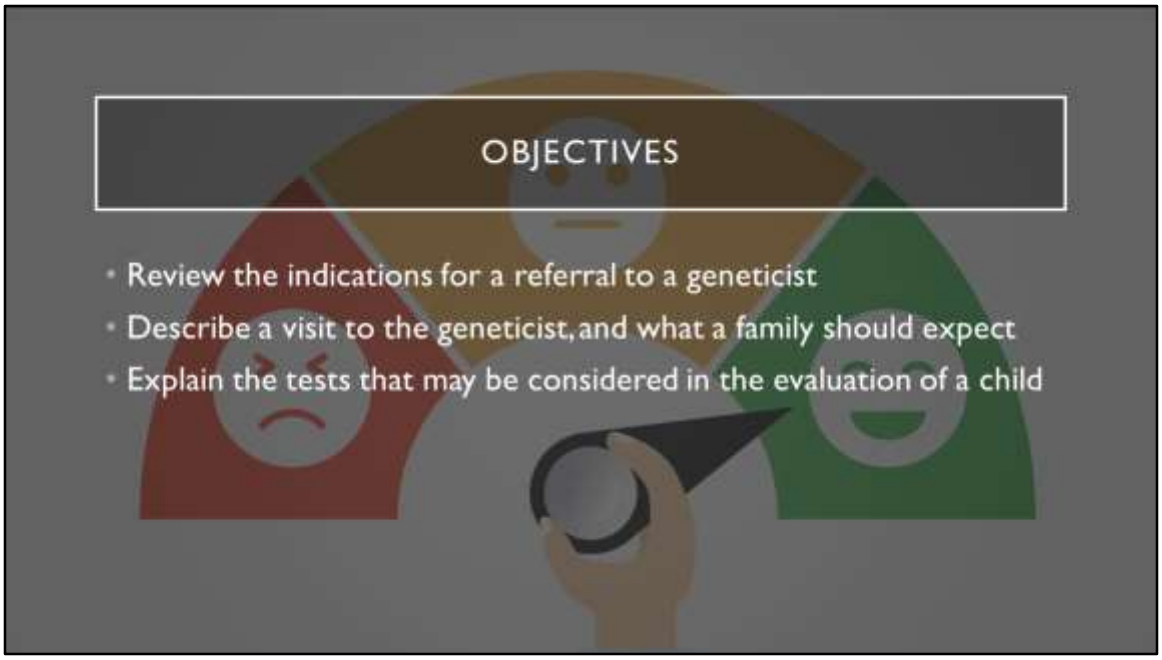
TEXAS
Health and Human Services

Early Childhood Intervention

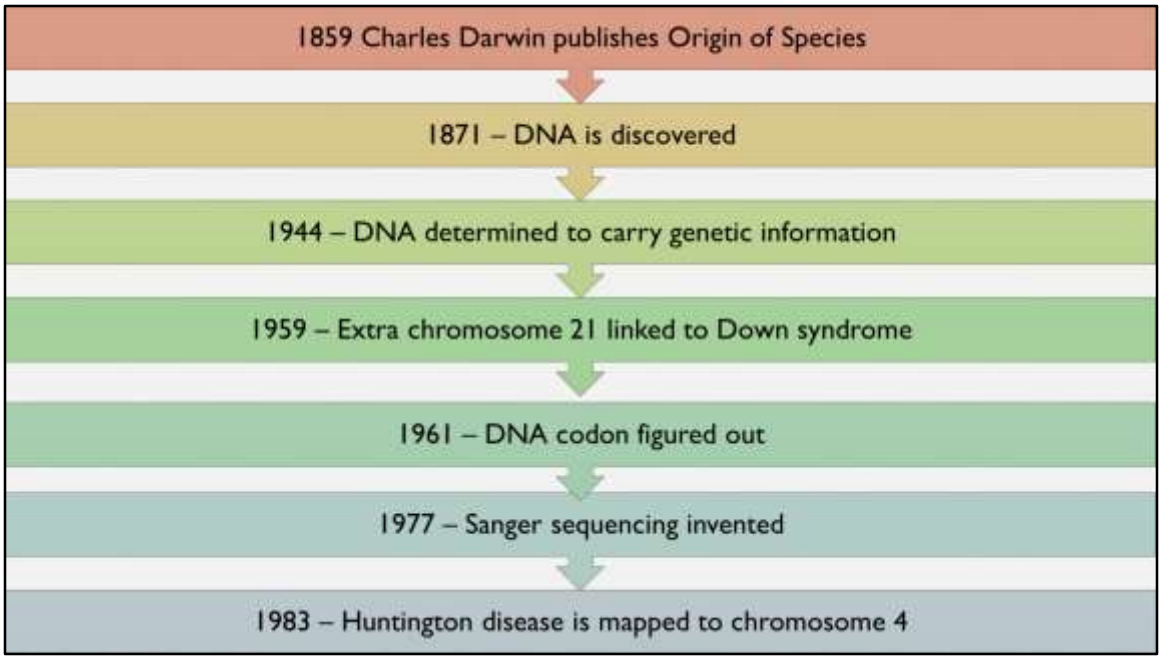
Genetics Webinar Series



- Today I will be presenting The Genetics Referral and Beyond. What you and more importantly your patients can expect from a genetics visit.



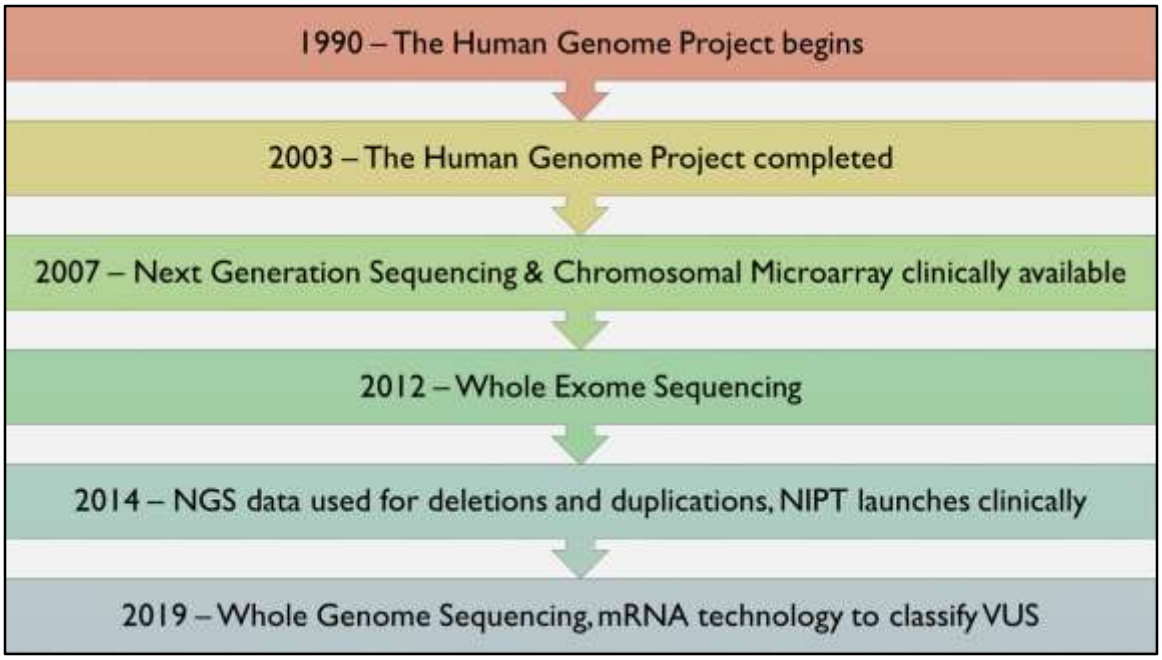
- My presentation is fairly straightforward, but is very relevant as there are many misconceptions regarding medical genetic. My hope is that this presentation will help you to have a better sense of what types of referrals you should send.
- Also, my hope is that by understanding the visit you will be able to prepare your families for the visit.
- And I also want to touch on genetic testing as it has changed quite a bit in a very short amount of time. And to best highlight the rapid changes in genetics I'd like first share with you some medical history.



- 1859 - Charles Darwin publishes Origin of Species

- 1871 – DNA is discovered, but we still didn't know what DNA was and it wouldn't be for 73 more years before…
- 1944 – DNA was determined to carry our genetic information
- 1959 – It was 15 years later that we could see chromosomes using special microscopes – and it was in 1959 that we realized an extra chromosome 21 was associated with Down syndrome
- 1961 – It wasn't until 1961 that we realized 3 nucleotides made a single codon for an amino acid in a protein
- 1977 – Sanger sequencing was invented initially using electrophoresis gels with very limited ability on the length of DNA that could be read at a single time; this would later be improved using special capillary electrophoresis tubes, fluorescent tags, and computers to speed up the fragment analysis
- 1983 – Huntington disease is the first disease to be mapped to a specific chromosome, by 1989 through linkage studies we figured out that the gene was probably close to the telomere (or the end) of the petite arm of 4. The candidate region was about 2 Mb; to put that into perspective if the human genome is the size of the earth and if a gene takes up a few city blocks then you are saying that

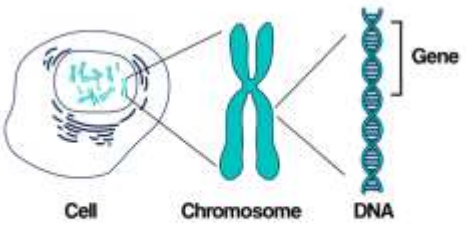
you can narrow the location of this gene to the city of Dallas. So it was good, but we were still several years away from actually finding the street that this gene lived on which was figured out in 1993.



- In 1990 an important international project called the The **Human Genome Project** (**HGP** began with the goal of determining the sequence of every single nucleotide base pairs that make up **human** DNA, and with that identifying and mapping all of the genes of the **human genome**. This project was projected to take 15 years to complete but ended 2 years early – with the sequencing completed from close to 3 billion nucleotides. we now know there are around 21,000 genes with currently somewhere between 3-5000 associated with human disease in some capacity.
- In 2007 started NGS and CMA became available. CMA doesn't actually seq the genome but looks to see if all of the genome is present, i.e. are there any deletions or duplications of the genome.
- In 2012 WES became available clinically and the first ones were taking approximately 6 months to sequencing and analyze the data. Within a couple of years 6 months turned into 4, then 3, then 2 and in urgent situations an exome can be obtained in less than 2 weeks which is astonishing when you think that less than 10 years prior we finish a project that took 13 years to sequence a genome.
- In 2014 we start to use NGS data in new ways and are able to determine not only the code using the data but also deletions and duplications. Around this time we also have new prenatal techniques which will replace the quad screen.

- And now today in 2019, we aren't just sequencing the protein coding regions of the genome but noncoding regions as well and using mRNA technology to classify variants.
- Things are changing at an exponential pace which may leave some people feeling…

"I DON'T THINK WE'RE IN KANSAS ANYMORE, TOTO."



- A bit overwhelmed.
- It is true that many of the things we were doing 10 years ago appear to be in the dinosaur age of medical genetics.
- The good news is that there is a field of medical genetics and we don't expect non-genetics providers to keep up with this pace of new knowledge.
- In fact, I hope to show you that given the complexities of genetics it's really best for medical genetics providers to take the lead when it comes to genetic diagnoses.

Every cell has DNA. DNA is the *same* in every cell.	Genetic diseases have similar severity amongst family members.
All mutations are bad.	Everyone with a genetic disease will have an identifiable mutation.
Genetic testing is needed to make a diagnosis for all genetic diseases.	Everyone with a mutation for a genetic disease will manifest disease.
Negative family history means a genetic diagnosis is unlikely.	Direct to consumer tests are accurate.

To highlight this – here are some misconceptions that we commonly debunk. All of the following are incorrect statements.

- Every cell has DNA – no, RBC don't have DNA; DNA is the same in every cell – no there are somatic mutations, mosaicism, DNA is also regulated differently in different cells at different times.
- All mutations are bad, not using this term, use variant instead
- Genetic testing is needed to make a diagnosis for all genetic diseases. – No we make a dx in things like NF1, BWS, Marfan, hEDS and many others
- Negative family history means a genetic diagnosis is unlikely. – No, there are many genetic diseases with a high new mutation rate. For example: 50% of people with NF1 are the first in their families to have NF1.
- Genetic diseases have similar severity amongst family members. – No, in tuberous sclerosis one family member may have abnormalities to their finger nails and another could have devastating infantile seizures.
- Everyone with a genetic disease will have an identifiable mutation. No, for example, 5% of people with Marfan syndrome will have no identifiable mutation.
- Everyone with a mutation for a genetic disease will manifest disease. No, there are many d/o with lower penetrance including one example I will share with you in a bit.

- Direct to consumer tests are accurate. – No, a recent study showed that over half of DTC results are either flat out wrong or interpreted incorrectly by the lab.

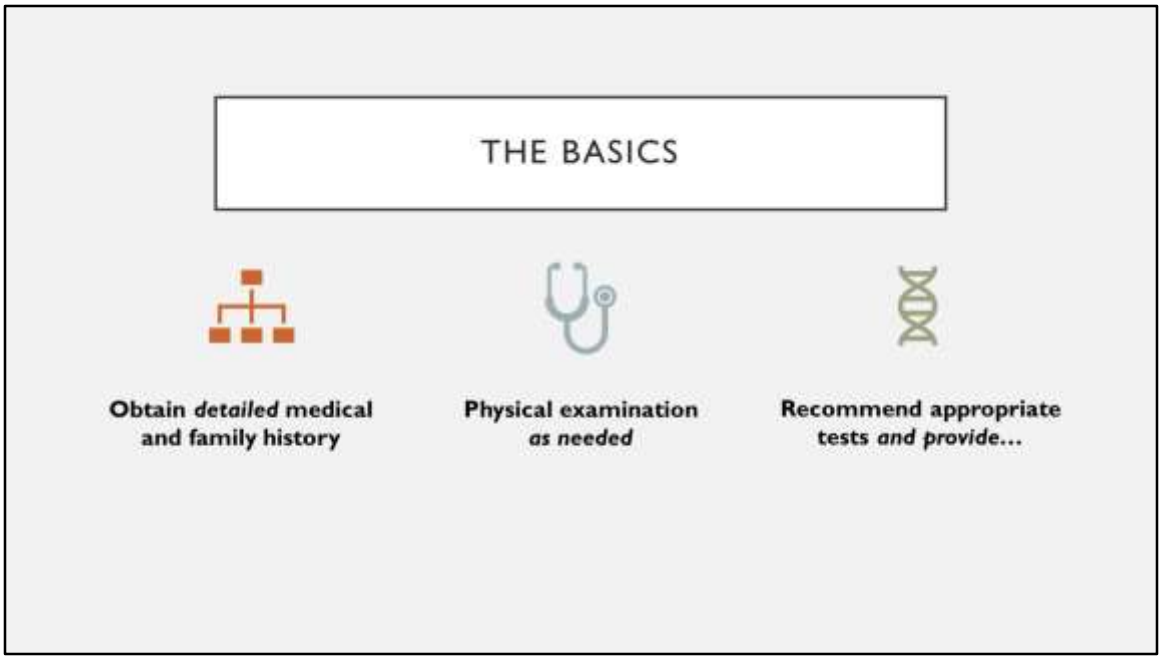
- For this reason I tell my students…

- Don’t order tests you don’t know how to interpret – it’s like picking your nose in public.
- It’s all fine until you get something and you don’t know what to do with it.
- And now you are in a situation where your patient may have a very long wait time before they can get appropriate counseling.

- Let’s switch gears and talk about the genetics visit.

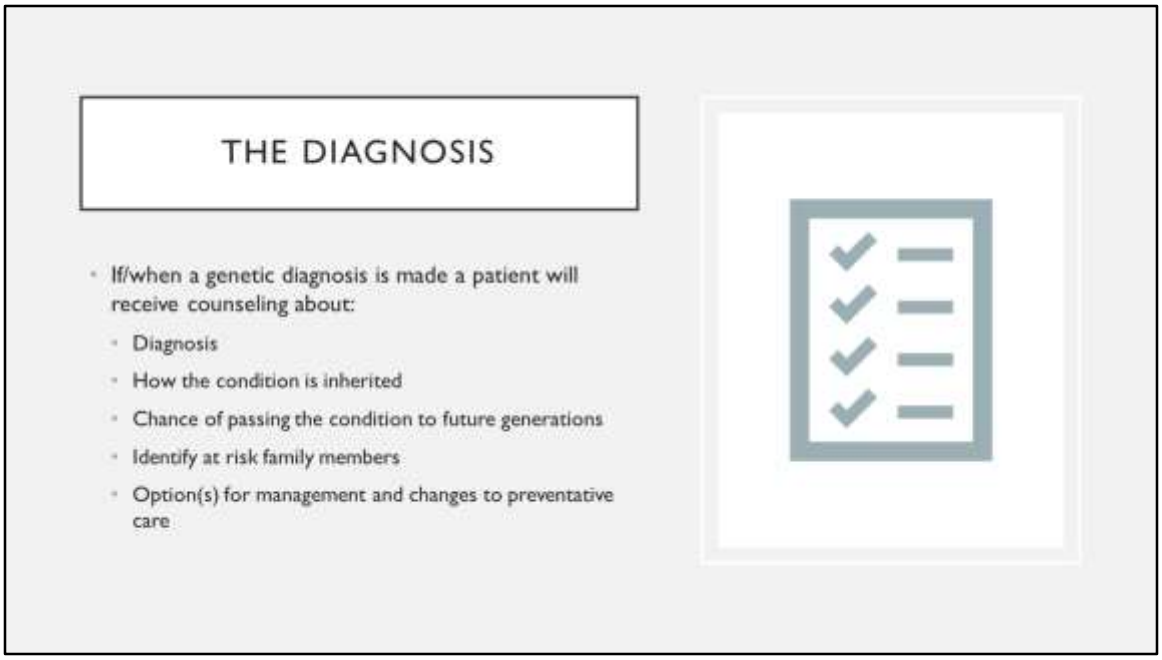
- Let's start with our team.
- Geneticists are medical doctors who see patients. The vast majority of us completed a residency in IM, peds, or OBGYN in addition to medical genetics. There is also now a further fellowship for biochemical genetics to care for pts with metabolic diseases.
- I try not to leave home without a genetics counselor. They are experts in not only the medical science but also in providing appropriate support and counseling to patients.
- Dietician with metabolic expertise
- Nurse coordinator
- Administrative staff front line and integral to the team, know how to find us the fastest and know how to triage needs
- +/- Trainees

- Most geneticists are in academic or large private institutions. Consultations take place in a clinic office or hospital.
- These meetings are most often in-person with individual patients or families, but the availability of telemedicine is expanding and this is especially helpful for patients who live in regions of the country with limited access to healthcare.



- Detailed medical and family history – I typically start with birth and go in chronological order; I'm trying to paint a picture of someone determining what pieces of their medical hx can be lumped together or split apart; in many cases we also need to know about development and education as well as psychiatric disease as this can often be part of an underlying genetic condition. We will also take a family hx and draw a pedigree.
- Detailed exam – looking for distinctive facial features. specific measurements may be taken and we may ask to take photos to add to the EMR
- We then may offer specific testing options…

- In my clinic patients receive verbal and written pretest counseling and can opt out of the testing at any time.
- We explain possible benefits of the testing as well as the limitations.
- They should be told what information the testing may give them and the information it does not provide.
- They should know if this information could impact other family members, as well as legal implications such as how this information could impact obtaining life or disability insurance.



If/when a genetic diagnosis is made a patient will receive counseling about:

- Diagnosis, prognosis
- How the condition is inherited
- Chance of passing the condition to future generations
- Identify at risk family members
- Option(s) for management

A GENETICS PROFESSIONAL

WILL

Interpret and communicate complex medical information

Help patients make informed, independent decisions about their health care and reproductive options

Respect individual beliefs, traditions, and feelings

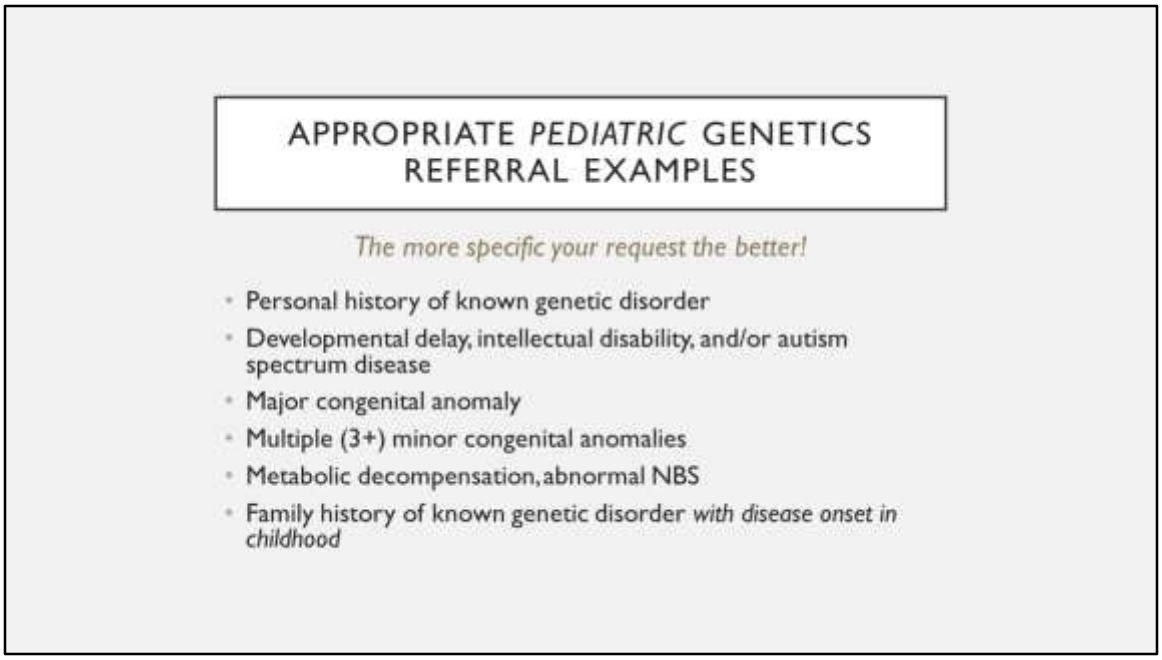
WILL NOT

Tell a patient what decision to make

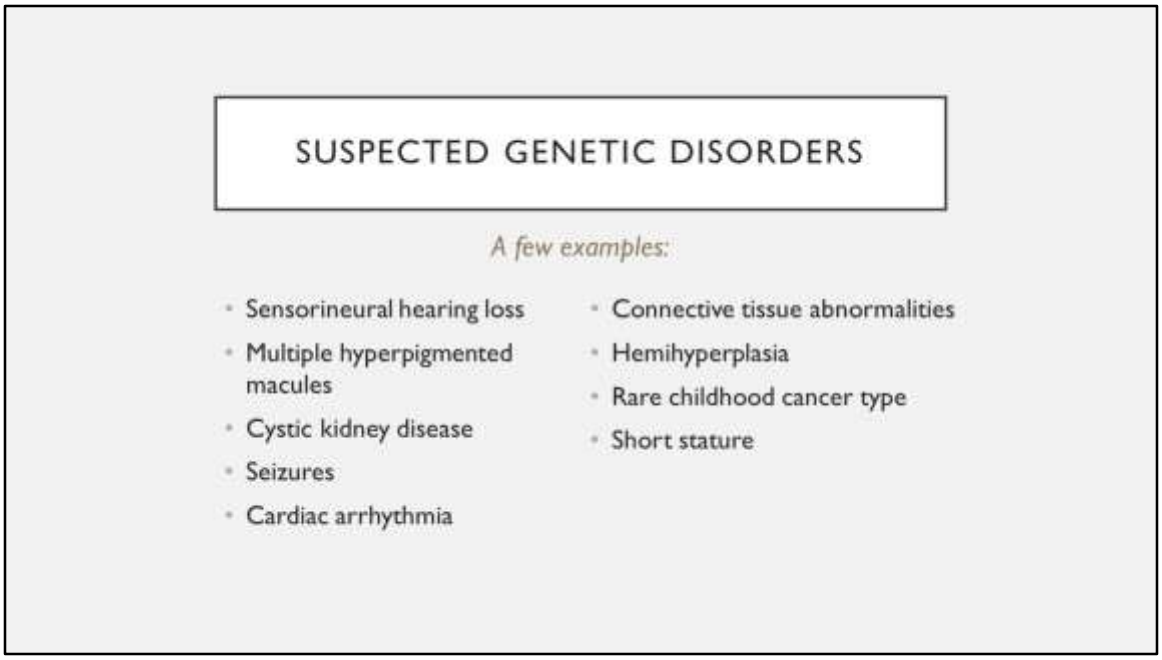
Advise a couple not to have children

Recommend a pregnancy be continued or terminated

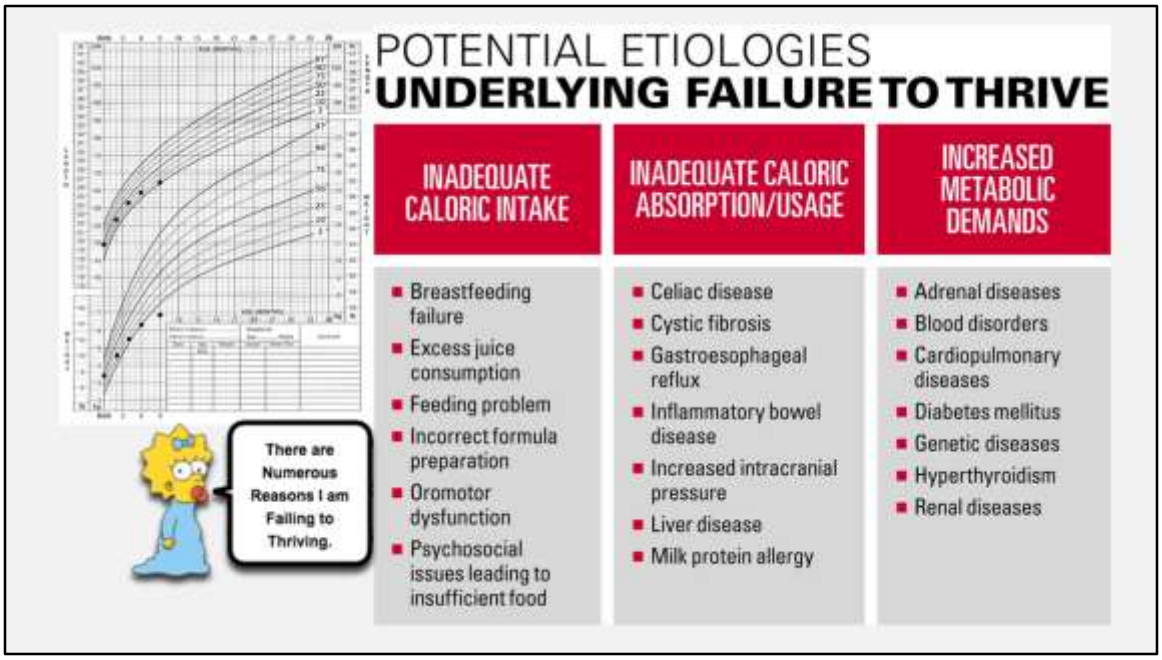
WHO TO REFER



- Personal history of known genetic disorder - perhaps they recently moved
- Developmental delay, intellectual disability, and/or autism spectrum disease
- Major congenital anomaly
- Multiple (3+) minor congenital anomalies - especially when associated with a specific genetic disease; most people have at least 2 minor anomalies; we also have normal variations in the general population that can be passed down by parents, an example of this would be epicanthal folds in someone of Asian ethnicity
- Metabolic decompensation, abnormal NBS
- Family history of known genetic disorder *with disease onset in childhood (we do not typically offer genetic testing for d/o with adult onset to children; we typically wait until they are old enough to consent to this testing themselves)*

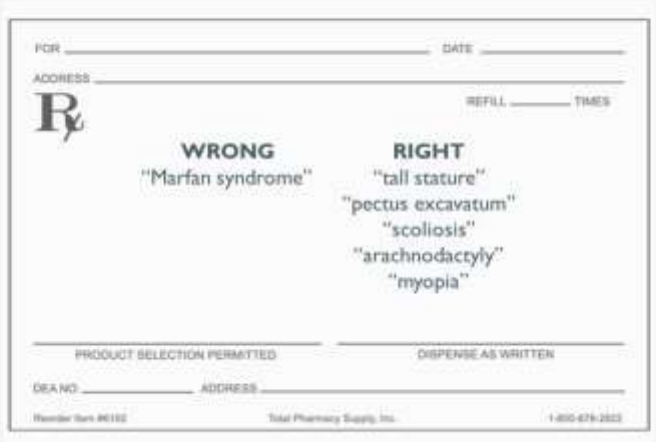


- No clear referral reason provided – this will also not help us triage urgency; the most enjoyable cases I have had have been when I'm working with other experts. I enjoy learning from them
- Initial work-up hasn't been done – FTT
- Distant family history of disease +/- affected person does not have a clear known diagnosis
- Family history of adult onset condition
- Disorder is not genetic – example Lupus

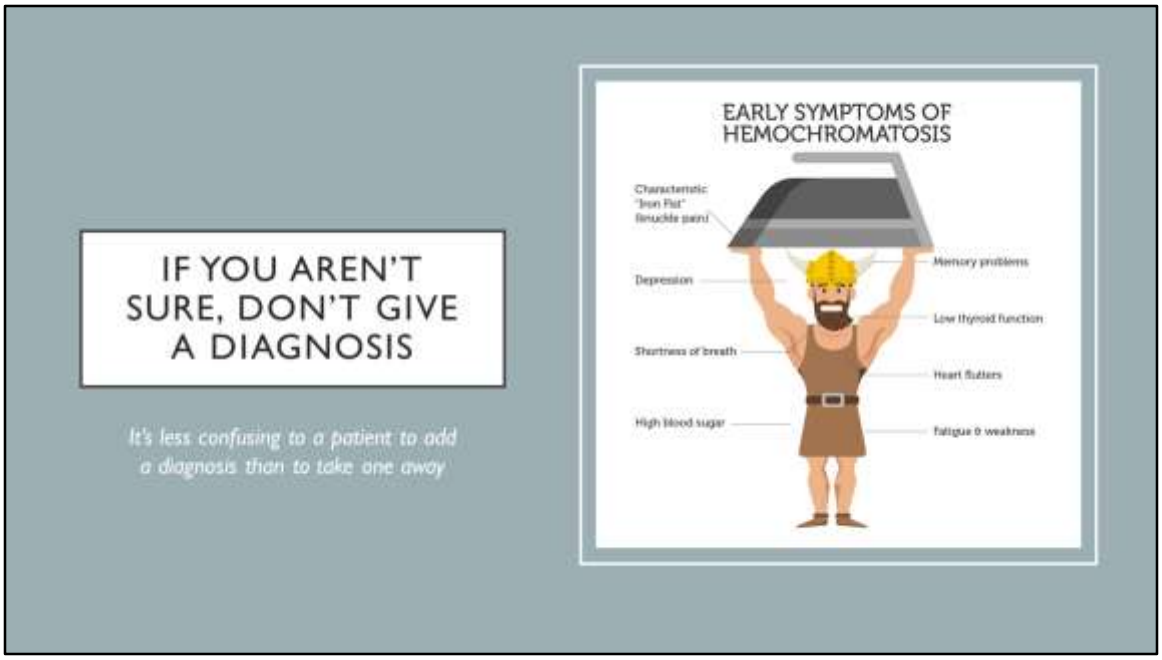


- No clear referral reason provided – this will also not help us triage urgency; the most enjoyable cases I have had have been when I'm working with other experts. I enjoy learning from them. occasionally I get a referral with no information and I'm not able to easily identify the question or concern that got them there. An example of this is "dysmorphic features" but none are listed and I don't really see any on exam
- Initial work-up hasn't been done – cases where genetics referral is premature and there are other more common etiologies for a problem than genetics; an example is FTT which we get from time to time; without prior work up, diet hx and malnutrition was the cause
- Distant family history of disease +/- affected person does not have a clear known diagnosis - we cannot provide appropriate testing options or risk assessment unless we know the disease
- Family history of adult onset condition, or it's a carrier status condition
- Disorder is not genetic – example autoimmune conditions such as Lupus, immunogenetics is still in its infancy and genetic testing is often not

If you suspect a genetic diagnosis, but it is NOT confirmed do not use it as your referring ICD-10 code



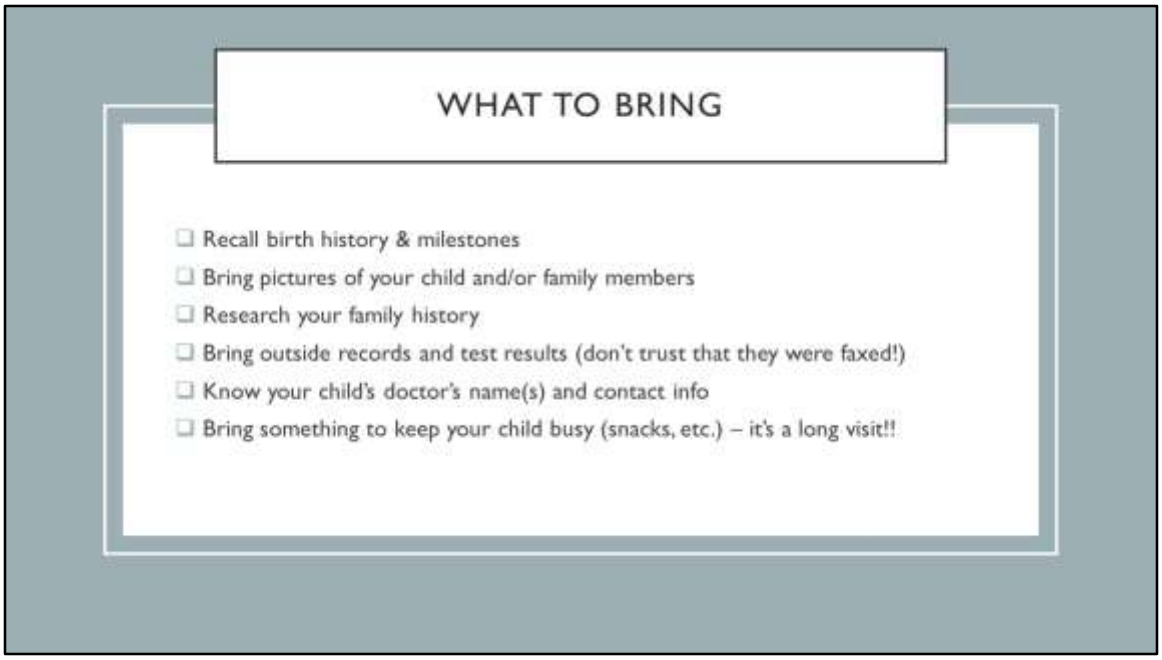
- This causes confusion
- Do they have it?
- Do they not?



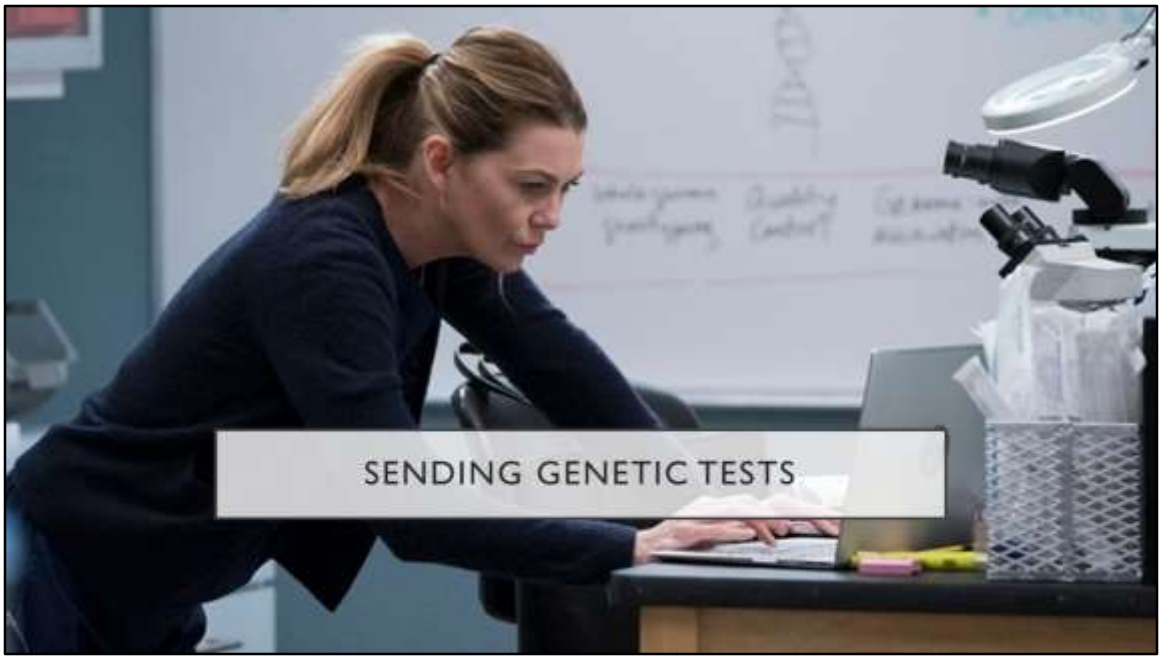
- Example:
- Patient had acquired low testosterone attributed to inadequate signaling from the pituitary, so this would be hypogonadotropic hypogonadism which is a feature of hemochromatosis.
- The provider got a family hx and found out the 10 yo child was dx with DM.
- They put these together and came up with the ddx that included hemochromatosis which is a progressive iron overload condition.
- They did get genetic testing which showed the patient was a carrier for a pathogenic variant (however this variant is not highly penetrant).
- The physician thought carriers could be mildly affected and told the patient to start getting treatment which is phlebotomy to remove blood.
- When I saw the patient I explained that they aren't affected, and it's estimated that around 1 in 10 people are carriers for this condition. Not only that but most people with two mutations never actually get the clinical disease bc it is so low penetrance.


HOW TO
PREPARE
YOUR
FAMILIES

- Tell the family WHY you think they should see a geneticist - Doesn't have to be specific or detailed, but they should know purpose.
- Longer wait times don't mean it's not important – patients may no show given perceived lack of concern.
- Visits are much longer than usual
    - Don't schedule other important things that day
    - Try to bring just the child and not other children as the visit is long
    - Both parents are appreciated, but if only one parent can come it's ideal if it is the primary caretaker
    - Unless explicitly told fasting is unnecessary



- Recall birth history & milestones
  - When did they sit, walk and talk? What was the birth weight and length?
- Bring pictures of your child and/or family members
  - Especially if a parent cannot attend, and if dysmorphic features are a concern
- Research your family history – what health conditions are in the family?
- Bring outside records and test results (don't trust that they were faxed!)
- Bring previous doctor's names and contact info
- Something to keep your child busy (snacks, etc.) – it's a long visit!!
- Try to bring just the affected child as other children can be distracting.



A little different than TV

GENETIC TESTING TABLE*

	**FISH	#G-band Chrom Analysis	^aCGH oligo	aCGH SNP	Southern	$ PCR/ Single gene sequencing	@Whole Exome Sequencing	mtDNA sequencing	mtDNA copy number	Analyte Screening
Aneuploidy	+	+	+	+	-	-	-	-	-	-
Chromosomal Microdeletion	+	If del is >4Mb	+	+	-	-	-	-	-	-
Chromosomal Microduplication	+/-	If dup is >8Mb	+	+	-	-	-	-	-	-
Balanced Translocation	+	+	-	-	-	-	-	-	-	-
Absence of Heterozygosity	-	-	-	+	-	-	+/-	-	-	-
Uniparental Disomy	-	-	-	+ Isodisomy (AOH)	+ Meth-specif digest	-	+/- Isodisomy (homo)	-	-	-
Triplet repeat Disorder	-	-	-	-	+ Large reps	+ Small reps	-	-	-	-
Methylation Abnormality (AS/PWS)	-	-	-	-	+ Meth-specif digest	-	-	-	-	-
Point mutation Nuclear-encoded gene	-	-	-	-	-	+	+	-	-	-
mtDNA point mutation	-	-	-	-	-	-	+/-	+	-	-
mtDNA depletion	-	-	-	-	-	-	-	-	+	-
%Metabolic	-	-	-	-	-	See below	See below	-	-	+

*The table is a guideline for genetic testing in a CLINICAL (i.e. not research) laboratory. **FISH testing requires a probe specific for the region in question. FISH testing is NOT test of choice for microdeletion/microduplication. # at least 550 band resolution. G-bands is NOT test of choice for microdeletion or microduplication. ^Oligo microarrays have exon by exon coverage for many genes and can detect small deletions or duplications of these exons. $many sequencing tests perform duplication/deletion analysis of the gene in question. @WES at BCM covers the mitochondrial genome. %Metabolic testing diverse and includes serum amino acids, urine organic acids, very long chain fatty acids, sterol profile and others. Testing specific for disorders within particular groups—e.g. organic acidurias, peroxisomal disorder, etc. Single gene sequencing and WES can detect mutations in genes responsible for many metabolic disorders.

There is not one test that does everything. This is a worksheet I give students and it's outdated.

Chromosomes – show you a karyotype
CMA
- Can show consanguinity (AOH), rape, etc.
- What is the duty to report for suspected sexual assault?

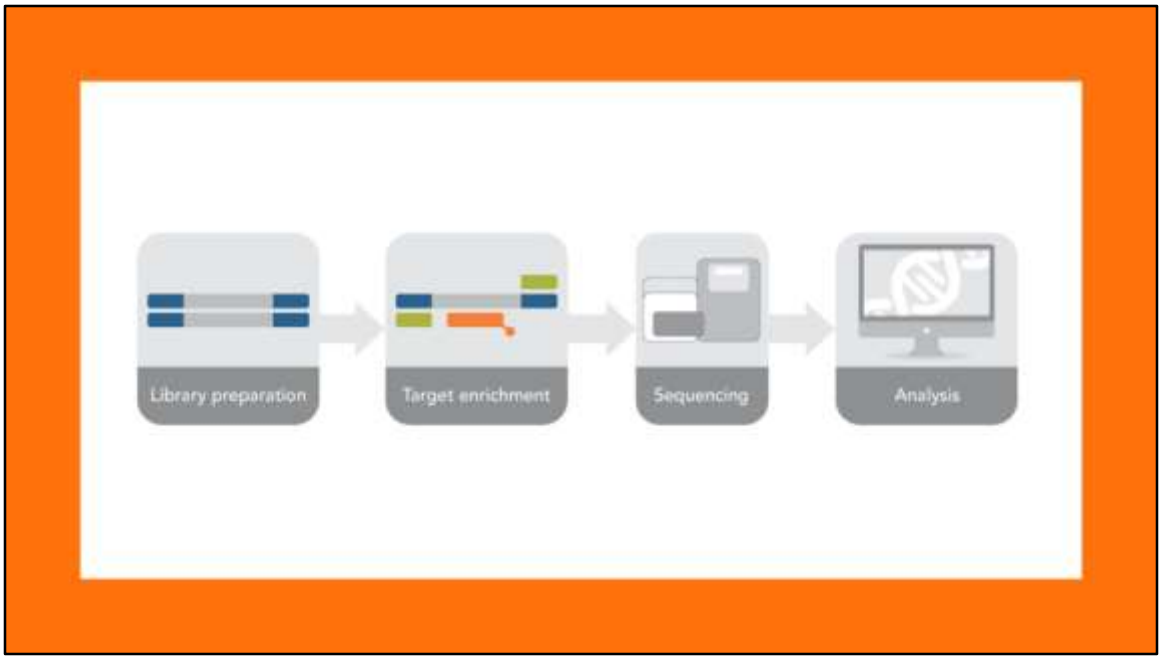
Sequencing Panels

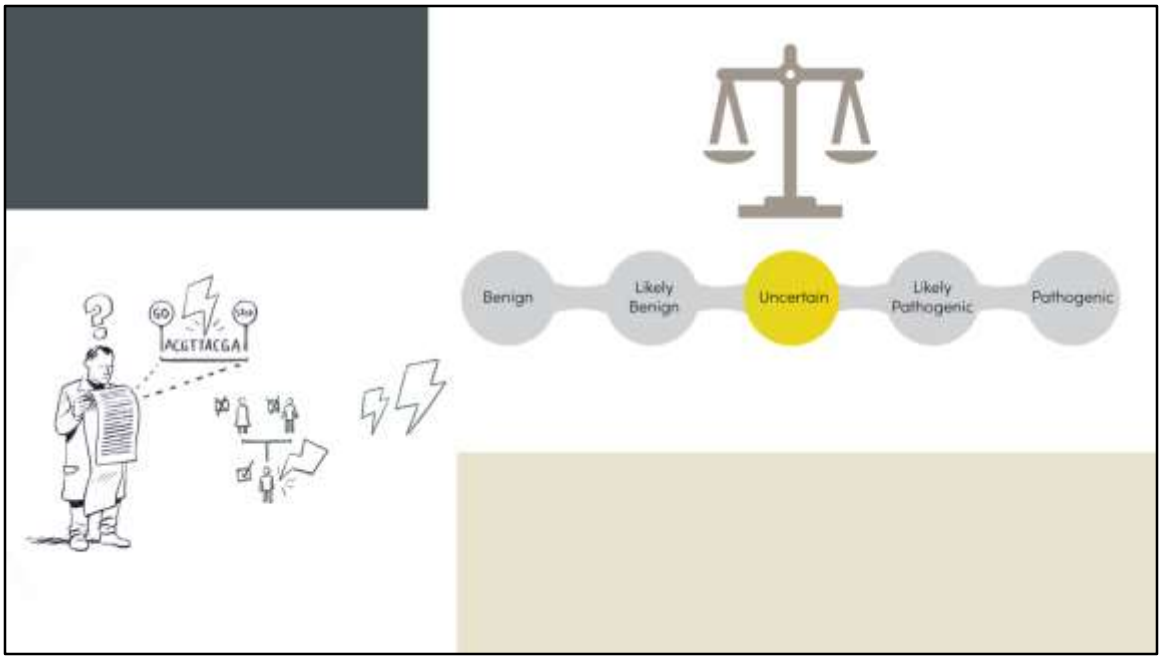
WES - Non-paternity

Triplet repeat d/o are not picked up on any of these, require other testing modality
Example: congenital myotonic dystrophy case

Long wait times are usually due

- Insurance limitations
- Prior auth
- Medicaid vs private insurance?
- Institutional billing or direct to the insurance? If I'm sending this through institutional billing what's the upcharge? Is there an oop?
- Does the lab I'm sending this bill private insurance? Do they bill Medicaid?
- In network or out of network?
- Medically warranted or not? (example: b-SNHL is covered, but u-SNHL is often not)
- Some tests require that they are done in certain order, 1st tier first, etc.
- Sent by genetics?
- Do I know the rep, can I get something for free?
- Which CPT codes to send?
- If you aren't sure, don't send as we may need that CPT code

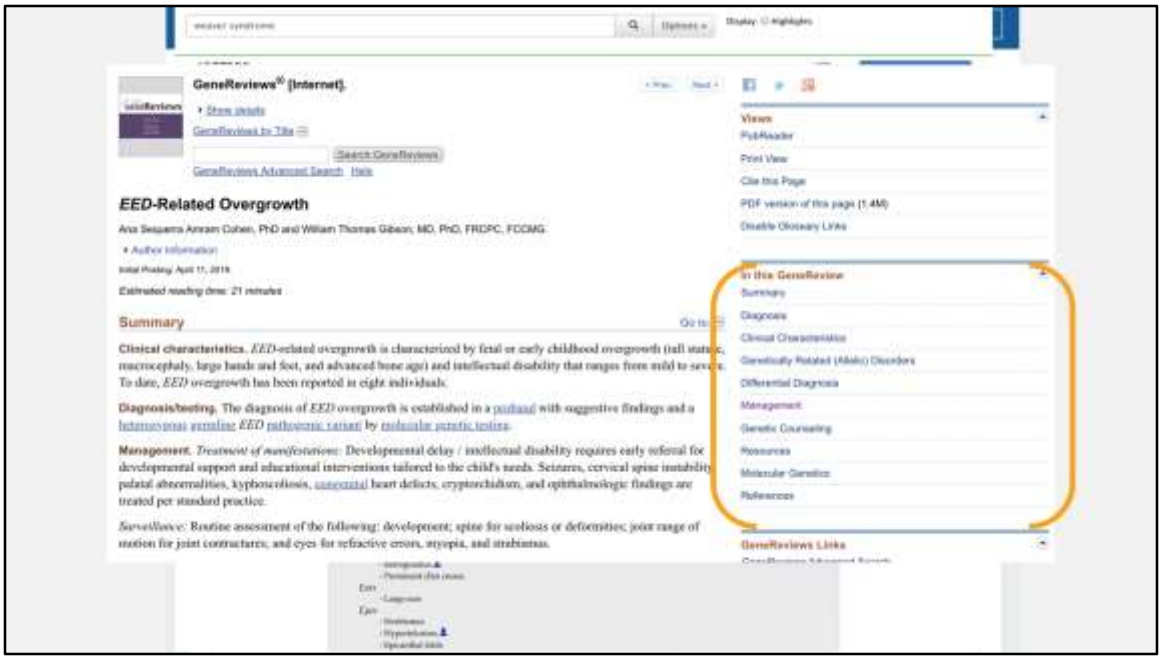

Library preparation
Target enrichment
Sequencing
Analysis



Genomic variants are classified on a 5 point scale to indicate the likelihood that particular variant is associated with human disease

- We will send our note
- We may need more visits
- We may discharge a patient without a diagnosis – this does not mean it's not genetic, it may mean that the current likelihood for figuring out a genetic dx is not very high meaning the yield of further testing is low; and so the benefits of trying to get an answer may not outweigh the cost to the family; for example: isolated GDD/ID/ASD after Fragile X, IEOM, and CMA is currently <5% to get a dx on WES (likely bc of polygenic, multifactorial, as well as nonspecific search term). That being said if the phenotype changes, for example: the patient with delays now has seizures we didn't know about before, send them back to us bc we have a new phenotype and can send more specific testing.
- If we have a diagnosis we will likely provide the patient with guidelines and/or resources and likely follow them
- *If you aren't sure, please ask!*

- If you aren't sure reach out to the genetics and ask
- You should rule out other causes of HTN
- EX: NF1 and HTN
- Preventative disease causes of HTN (overweight, high sodium intake, etc)


GeneReviews® [Internet].
Show details
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Search GeneReviews
GeneReviews Advanced Search Help
EED-Related Overgrowth
Aria Sequeira Amram Cohen, PhD and William Thomas Gibson, MD, PhD, FRCPC, FCCMG
Author Information
Estimated reading time: 21 minutes
Summary
Clinical characteristics. EED-related overgrowth is characterized by fetal or early childhood overgrowth (tall stature, macrocephaly, large hands and feet, and advanced bone age) and intellectual disability that ranges from mild to severe. To date, EED overgrowth has been reported in eight individuals.
Diagnosis/testing. The diagnosis of EED overgrowth is established in a proband with suggestive findings and a heterozygous germline EED pathogenic variant by molecular genetic testing.
Management. Treatment of manifestations: Developmental delay / intellectual disability requires early referral for developmental support and educational interventions tailored to the child's needs. Seizures, cervical spine instability, palatal abnormalities, kyphoscoliosis, congenital heart defects, cryptorchidism, and ophthalmologic findings are treated per standard practice.
Surveillance: Routine assessment of the following: development; spine for scoliosis or deformities; joint range of motion for joint contractures; and eyes for refractive errors, strabismus, and strabismus.
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