Genetic Testing: Should I do it?

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What is the diagnosis?!
Sometimes not that easy!
Down Syndrome

trisomy 21 (92-95%)
translocation (3-6%)
mosaicism (1-4%)
Sometimes it’s not that easy!

PAX6

mutation in the gene

sequencing

del/dup

inside the gene

WAGR

deletion between PAX6 and WT1

...or others!
Sometimes you get surprises!
Very little view: Aniridia
CCT unable to measure (> 1000)
Cycloplegic refraction not possible
Discs were barely visible but cupping was evident OS > OD

…order testing for WAGR
Genetic Testing Results

6p25.1 interstitial duplication

FOXC1 gene

Parents microarray normal
Posterior embryotoxon
Aniridic form of Ax-Rieg

No risk for Wilms
No risk for retardation or GU issues
No risk for macular hypoplasia, cornea etc
better visual prognosis
It gets more difficult...
It gets more difficult...

Half brother (same mom) has ARS!
Mom normal
no duplication
= gonadal mosaicism
WAGR syndrome: del11p13

Balanced translocation

donor egg
Single gene testing

Must be easier!?
Rhodopsin gene ($RHO$)  
C to G @ nucleotide 249

*Is this causing the patient’s disease?*
Interpretation

mutation vs polymorphism
prior reports
prediction program
biologic prediction (proteomics)
changes in same codon
conserved base pair/codon
nearby reported changes
downstream nonsense/frameshift
segregation
What does a negative test mean?
Negative tests

Karyotype
change too small to see
micro del/dup
low mosaicism
not an aberration
faulty sample
specimen mixup!
Negative tests

Microarray

not a del/dup

translocation without CNV

resolution not small enough

specimen mixup!
Negative tests

Gene sequencing
what was sequenced?
hot spots?
exons?
exon-intron boundaries?
deep introns?
Negative tests

Gene sequencing
  del/dup
  right disease, wrong gene
    or not discovered
  wrong disease
  technical error
  specimen mixup!
Negative tests

WES/WGS

del/dup

wrong filter

same errors as sequencing
Negative tests

Any test

wrong diagnosis

non genetic

specimen mixup
Other issues...
40 y/o woman with AD RP

20 year old sister
  Will I get it?
5 year old son
  Will he get it?
Predictive Testing

Treatable/Preventable disease vs. Untreatable Disease
Predictive Testing

Benefit vs Harm
Predictive Testing Model

Huntington Disease

$(CAG)_n \ 4q$
Predictive Testing Literature

nonocular - lots
    HD, cancer, CF...
ocular - very little
+Predictive Testing: Pros

- reduced anxiety/uncertainty
- allows preparation
- life style changes?
- treatment/intervention
- identify others at risk
Predictive Testing: Cons

- emotional breakdown/suicide (rare)
- depression/anxiety
- burden/guilt
- unable to act on wishes
  - $, time, duties...
- unequal treatment
- restricted opportunity
-Predictive Testing: Pros

reduced anxiety/uncertainty for self & offspring
-Predictive Testing: Cons

depression/anxiety
burden/guilt
disappointment
  altered life plan
  other problems persist
unable to act on wishes
unequal treatment (pos or neg)
Predictive Testing of Children

confidentiality
privacy
individual justice
altruism

Who makes the decision?
Not ready for prime time

disпр misinformation 10
disпр misinformation 10

disпр misinformation 10

disпр misinformation 10

example: AMD genetic testing

Stone E: Genetic testing for age-related macular degeneration not indicated now. JAMA Ophthalmol 2015
AMD testing – why not?

- hard to interpret
- no clear effect on Rx
- may alter behaviours incorrectly
Pre-test counselling

risks

- non paternity
- other family discoveries
- emotional cost
- financial cost
- what does pt/family want to know
  - or not know?
- turn around time vs need
- confidentiality/disclosure
  - who will know?
  - insurance risks
- specimen handling
  - destruction
- other uses (research)?
Post-test counseling

Prognosis
What to look for
Treatment possibilities
Recurrence risk/inheritance
  reproductive options
Consent to share with others
Who else to test
Support groups/resources
Open door for the future
Recontact permission and expectations
Letter to pt/family and doctors
Counseling

Takes time!
So...

Do you want to do this??!!
What’s my point?

Genetic testing is hard!!

(even when you know the diagnosis)
Genetic testing

Is a process
Requires counselling
Is complex and difficult

But the ends justifies the means!
Help!!!

What test do I order?
What do the results mean?
What does the patient need to know?

…..Ocular genetics!
Which test?

Phenotype
Phenotype
Phenotype!!

...rare disease doctors
If you have a diagnosis

do the test for that diagnosis
Order the smallest most focused testing first
then tier outwards
Unknown diagnosis

more than one organ system
karyogram
microarray
is it similar to something else?
candidate gene?
panel for disease category?
one to two diagnoses?
can test for one
Unknown diagnosis
Tests negative
No Candidate test

Whole exome sequencing
exome slice
whole mitome
Whole genome sequencing
Don’t order a test if you don’t know what to do with the results!
Test interpretation

mutation vs polymorphism
segregation
pathogenicity
biologic prediction
in silico
data bases
proteomics
allele frequency
But it’s free!!

Large free panels
absence of in person counselling
false genome rate
unintended consequences
still have to interpret!!
But it’s free!

YOU GET WHAT YOU PAY FOR!
Need an
OCULAR GENETICIST
&
Genetic Counsellor!
But I don’t have access

- clinical genetics
- neurogenetics
- fellowships
  - ocular genetics
- genetic counsellors
- observerships
But DON’T

give poor care!

would you do brain surgery?
would you deliver a baby?
should you do genetic testing?!