The Gene New Deal:

What Can Save Us From the Rising Tide of WGS?

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Introduction

- What is the Gene New Deal? Catchphrase for WGS for all!
- Goal: Understanding what current clinical tests are amenable to WGS
- Examples: strengths and weaknesses of current clinical testing
- Data: ~12 years of testing at the Wisconsin State laboratory of Hygiene
- WGS : Assuming standard 40X short read sequencing

Conclusions

- WGS will likely identify the majority of structural abnormalities (studies needed)
- The power of karyotyping and FISH is clonal resolution
- Clonality and phasing lost with standard WGS sequencing and molecular tests
- A large proportion of molecular testing is not amenable to standard WGS
- Patients usually have multiple tests exceeding $1000
- Converting tests to NGS could result in significant cost savings

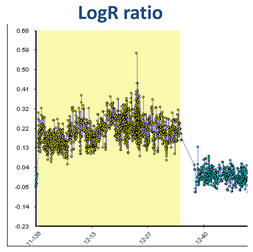
Examples

Case 1: Mild Pallister-Killian

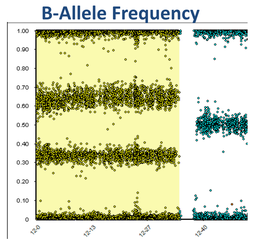
Newborn infant male
Prenatal
- Tortuosity of aorta
- Polyhydramnios
- Normal NIPT

Neonatal
- aortic valve thickening
- abnormal mitral valve

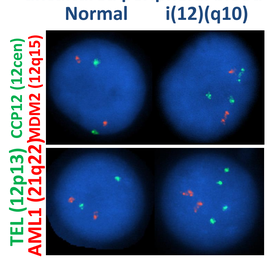
LogR ratio



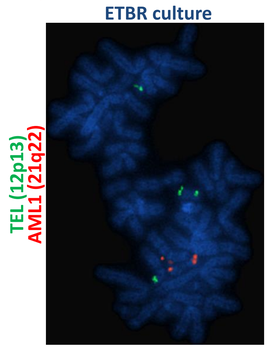
B-Allele Frequency



uncultured peripheral blood
Normal i(12)(q10)



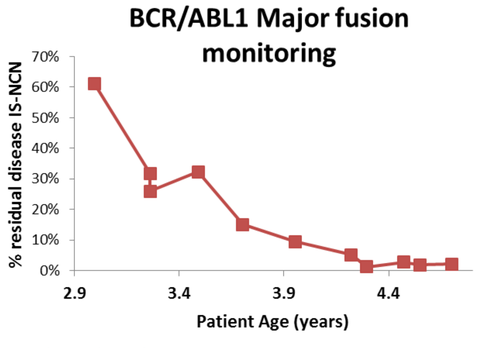
ETBR culture



Strengths and weaknesses
- Whole genome assessment (array)
- Loss of mosaic information (array)
- Chromosomes require growing cells (i(12)(q10) inhibits growth)
- FISH – mosaicism observed and i(12)(q10) confirmed

Case 2: B-cell ALL

~11 month old male infant
B-cell acute lymphoblastic leukemia (~11 mo.)
Chronic myeloid leukemia (~3 yr)

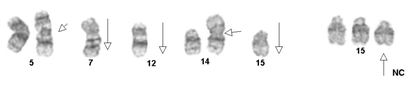


Strengths and weaknesses
- Very low copy number detection
- Specific, fast, inexpensive (relatively)
- Must know target a-priori

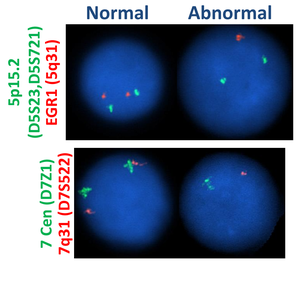
Case 3: B-cell lymphoma

78yr male with diffuse large B-cell lymphoma, pancytopenia

Karyotype 1 Karyotype 2



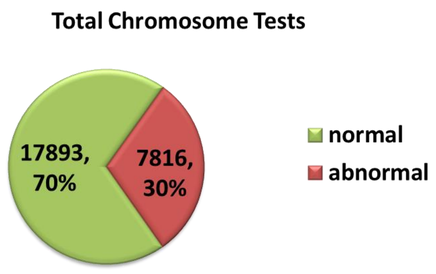
FISH

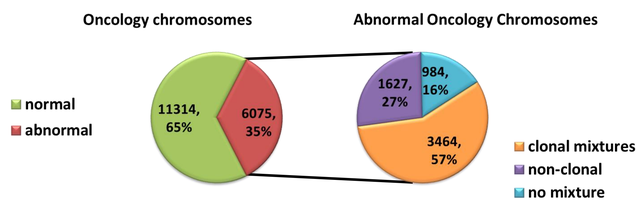


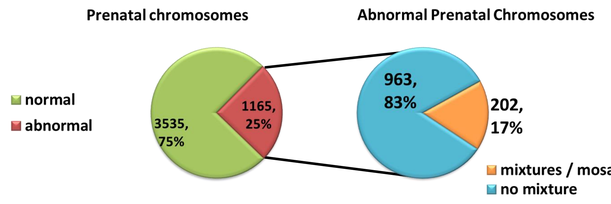
Strengths and weaknesses
- Whole genome assessment (karyotype)
- Cell clones detectable
- Low throughput, low resolution
- Can see Robertsonian and special translocations (karyotype)

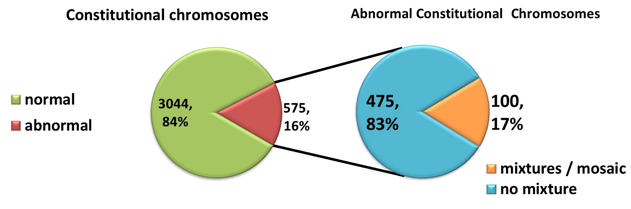
Results: 12 years of testing at WSLH

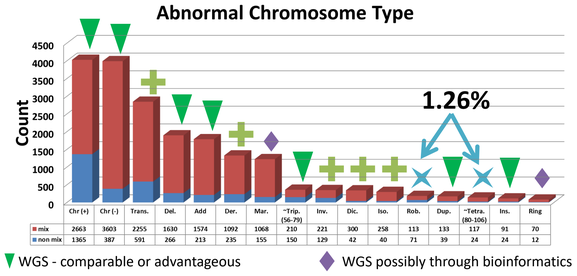
Chromosome analysis





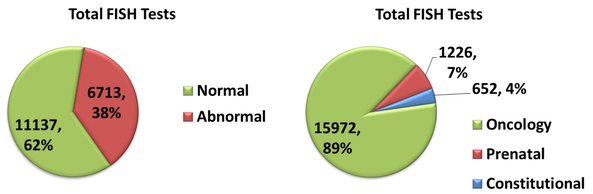


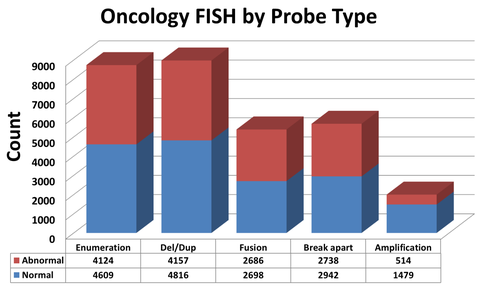


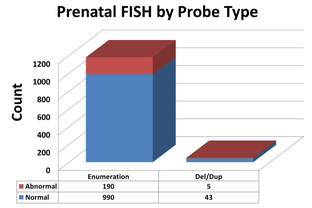


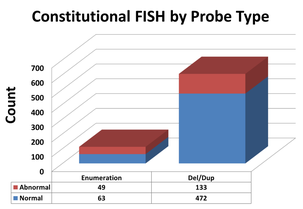
The average karyotype has three TYPES of abnormalities per case

FISH

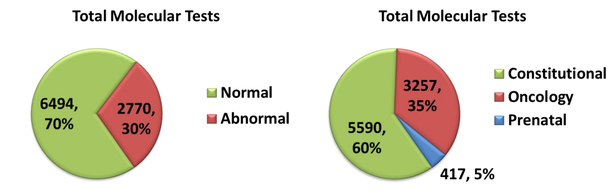


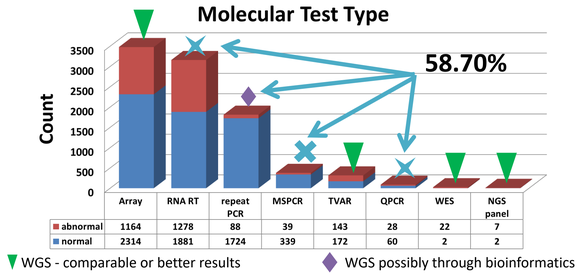




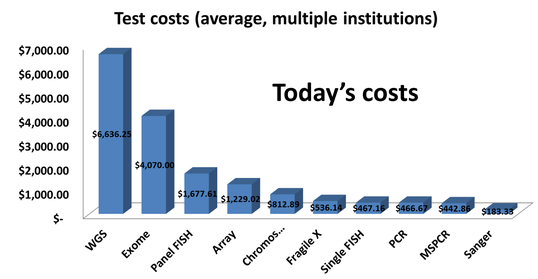


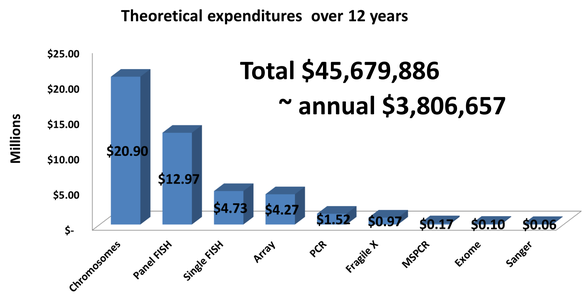
Molecular testing

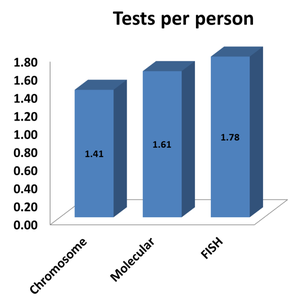




Cost analysis







NGS read equivalent cost estimates

Test type	Comparable read counts	NovaSeq cost equivalents	run equivalents
Sanger (2F + 2R 600bp)	8	$ 0.0000123	2500000000
Single FISH (200 cells, 2 probes 400X)	800	$ 0.0012312	25000000
Panel FISH (200 cells x 6 probes)	2400	$ 0.0036936	8333333
MSPCR (+3 CNTL) (4 probes 1000X)	4000	$ 0.0061560	5000000
Fragile X (2 probes 1000X x3 CNTL)	6000	$ 0.0092340	3333333
PCR (+3 CNTL) (4 probes 10000X)	40000	$ 0.0615600	500000
Chromosomes (1000 probes 40X)	40000	$ 0.0615600	500000
Array (750K probes 100X)	75000000	$ 115.4250000	267

based on $30,780 for highest output NovaSeq run list price

What will be happen if we don't implement the Gene New Deal?

- Delay understanding human diversity and disease
- Many will go undiagnosed
- Delay getting variants out of VUS land
- Delay personalized medicine
- We cannot fix what we don't know is broken

Questions

- Who can benefit from WGS?
- Clonality vs. exact alterations: what is more important for personalized oncology treatment?
- Will long read sequencing overcome short read challenges?
- What is inhibiting uptake of clinical WGS?
- How can we reduce WGS costs?