What's New in the NICU: Genetics Edition

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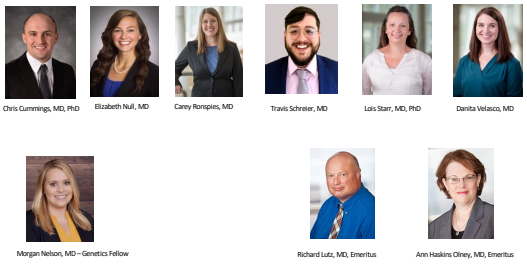

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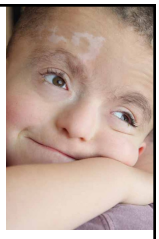
- 32w3d GA infant born to a 22 yo G2P0010 mother
  - 12 wk loss
- CNS malformation detected in utero
- Maternal cholestasis, thrombocytopenia
- No prenatal genetic testing
- No reported exposures
- Mom passed 1-hour GTT
- Labor was induced due to worsening
- Mother received antenatal steroids prior to delivery
- Resuscitation included CPAP --> PPV --> intubation at delivery
- Apgars 6 / 6 / 7 / 9
- Baby admitted to Bergan Mercy NICU
- Attempted extubation at 2 hours of life
- Reintubated with administration of surfactant
- Genetics was consulted for CNS malformation
- NBS pending
- 3 healthy paternal half sisters
- What testing should we recommend?



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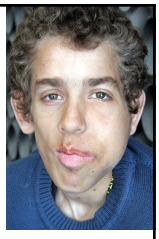
- What (7+ types) genetic tests do we send in 2025?
- Why do we send them?
- When do we send them?
- How do we send them?

- What genetic tests do we send most in the NICUs in September, 2025?



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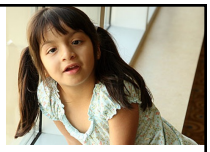
- Do most NICU parents consent to testing?



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What can the NICU do to help their geneticist?

- Consent family for us to see them
- Alert us to social issues
- Reinforce how incredibly helpful parent samples are to family
- Don't put too much water in the genetics bucket
- Help families understand that we may call with results to deliver them timely.
- Genetics testing is not for us – it is for the family. It is not helping 'our research'. This is for them, no one else is benefiting.
- Know that blood is ideal for the proband d/t slightly improved fail rate. Do not hesitate to ask us to approve buccal if that is best for your patient or more comfortable for the parents.

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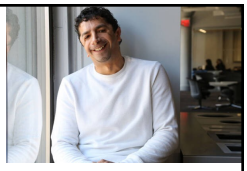

- What is critical to consider prior to sending an exome or genome study?

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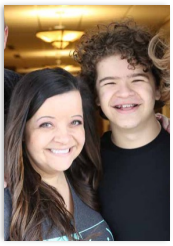

- Important things to consent a family for prior to ordering genetic testing
  - Uncertain variants
  - Disability/Life insurance
  - Non parentage
  - Close relationships
  - Secondary ACMG findings

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- APC – Familial adenomatous polyposis
- RET – Familial medullary thyroid cancer
- BRCA1, BRCA2, PALB2 – Hereditary breast and/or ovarian cancer
- SDHD, SDHAF2, SDHC, SDHB, MAX, TMEM127 – Hereditary paraganglioma–pheochromocytoma syndrome
- BMPR1A, SMAD4 – Juvenile polyposis syndrome
- TP53 – Li–Fraumeni syndrome
- MLH1, MSH2, MSH6, PMS2 – Lynch syndrome
- MEN1 – Multiple endocrine neoplasia type 1
- MUTYH – MUTYH-associated polyposis
- NF2 – Neurofibromatosis type 2
- STK11 – Peutz-Jeghers syndrome
- FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11 – Aortopathies
- PKP2, DSP, DSC2, TMEM43, DSG2 – Arrhythmogenic right ventricular cardiomyopathy
- RYR2, CASQ2, TRDN – Catecholaminergic polymorphic ventricular tachycardia
- BAG3, DES, RBM20, TNNC1, TNNT2, LMNA, FLNC, TTN – Dilated cardiomyopathy
- CALM1, CALM2, CALM3 – Long QT syndrome types 14 and 16
- COL3A1 – Vascular Ehlers–Danlos syndrome
- LDLR, APOB, PCSK9 – Familial hypercholesterolemia
- MYH7, MYBPC3, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, MYL2 – Hypertrophic cardiomyopathy
- PLN – Intrinsic cardiomyopathy
- KCNQ1, KCNH2 – Long QT syndrome types 1 and 2

2025 ACMG v3.3

- BTD – Biotinidase deficiency
- CYP27A1 – Cerebrotendinous xanthomatosis
- GLA – Fabry disease
- OTC – Ornithine transcarbamylase deficiency
- GAA – Pompe disease
- ABCD1 – Adrenoleukodystrophy
- HFE – Hereditary hemochromatosis (C282Y homozygous)
- ACVRL1, ENG – Hereditary hemorrhagic telangiectasia
- RYR1, CACNA1S – Malignant hyperthermia susceptibility
- HNF1A – Maturity-onset diabetes of the young
- RPE65 – RPE65-related retinopathy
- ATP7B – Wilson disease
- TTR – Hereditary transthyretin amyloidosis

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Genetics consult – where can I request one?

How are the hospitals handling the financial-side of genetic testing?

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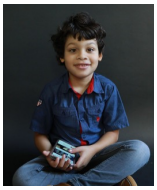
What is the *real* difference between ES and GS

- Exome (ES): ~1–2% coding regions
  - Great for coding SNVs/indels; our utilized labs call exon-level CNVs
  - We can usually add mtDNA without extra cost
  - 25-50% diagnostic rate in most NICU settings depending on phenotype target
- Genome (GS): all nuclear DNA ± mtDNA
  - Better for CNVs/SVs; noncoding/regulatory and splice variants
  - Includes many TNRs!
  - Can infer some structure
  - 35-50% diagnostic rate in most NICU settings depending on phenotype target
- Some diff dx sit fine with ES, some areas have up to 15% increased diagnostic rate with genome
- Cost
- Both miss: most repeat expansions, some mosaicism; consider RNA/long-read if suspected
- Rapids – 4 – 10 days for prelim



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Costs

- Rapid genome- $4000
- Standard genome- $4000
- Rapid exome- $3500
- Standard exome- $2500
- Rapid Aneuploidy FISH $2500
- Episign $1500 - $2500
- Karyotype - $1000 - $2500
- Panels - $300 - $2000
- Microarray - $1500 - $3000

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Are microarrays and panels dead?

- In the NICU?
- Microarrays and panels aren't dead, but we need to think about why if those are of interest we would not order a phenotype-guided ES/GS
- I still use panels in some distinct settings or to 'work backwards'

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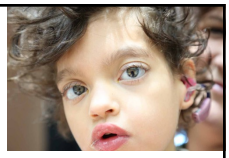
Things that still surprise me



- 1/10 families mention that they are happy to help our research
  - don't seem to recognize this as clinical testing
- Focus on cost
- 99/100 genetic consults are appropriate
  - Who are we missing?
- Fail rate
- Increase in IDM with MCA

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Homozygous likely pathogenic variant in *MMACHC* associated with methylmalonic aciduria and homocystinuria, cblC type

- Ammonia checked and bounced between 19-80
- B12 IM injections qd
- Baby showing improvement
- Lifelong treatment
- Recurrence risk, accurate counseling for parents
- Doesn't explain the reason genetics was consulted to begin with

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GENETICS NICU

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