Genomic Testing of Newborns: Bowl of Cherries or Can of Worms?

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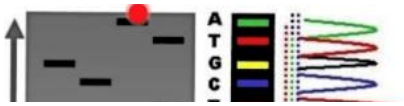
Disclosures

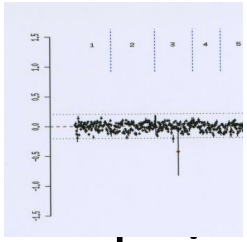
- Nothing to disclose

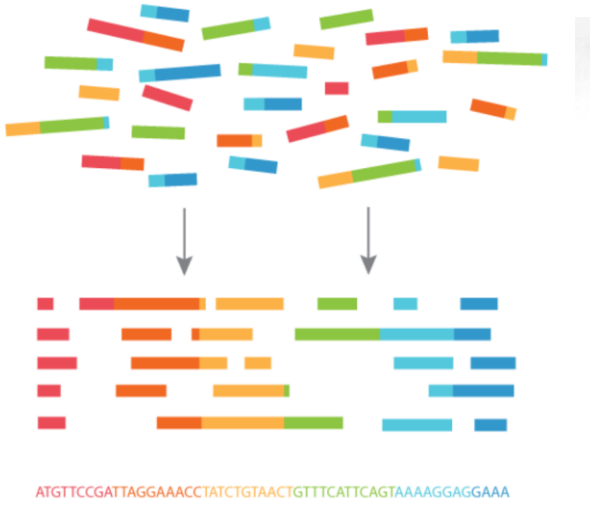
Populations

- Preimplantation Genetic Diagnosis
- Prenatal/During pregnancy
- Neonatal (1st month)
- Infant/Child
- Adolescent
- Adult

Genetic Testing







- Cytogenetic
  - Chromosome analysis
  - Chromosome microarray analysis
- Sanger/Direct Sequencing
  - Targeted single gene testing
- Next Generation or Massively Parallel Sequencing
  - Diagnosis-based gene panel
    - Genetically heterogeneous syndrome: “colon cancer”
    - Symptom-based: “seizures”
  - Whole Exome Sequencing
  - Whole Genome Sequencing

} Non-Hypothesis Based Testing

Variant Interpretation

- Pathogenic
- Probably Pathogenic
- Variant of Uncertain Significance
- Probably Benign
- Benign

Richards et al, Genetics in Medicine, 2015 May;17(5): 405-424

Diagnosis vs Screening

- Diagnostic testing
  - Patient based
  - Goal is to identify or confirm this patient's problem
  - Context of the Doctor-Patient relationship
  - Result is normal or abnormal
- Screening testing
  - Population based
  - Goal is to identify those at risk who need further testing
  - Public Health context
  - Result shows increased or decreased risk
    - Specific follow-up diagnostic testing is necessary

Topic

- Non-hypothesis based genomic screening testing in newborns

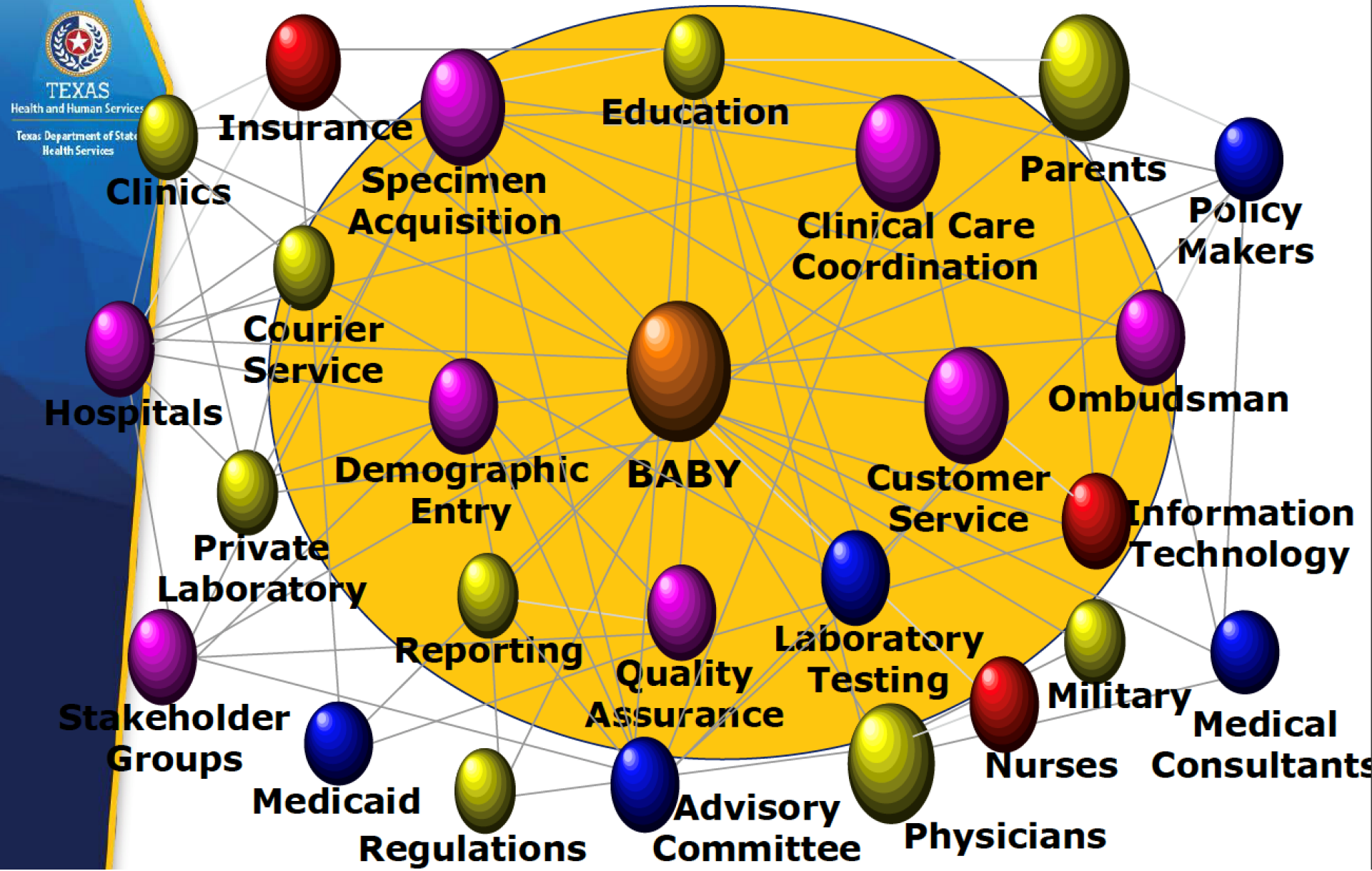
- Whole Exome/Whole Genome (WES/WGS)
- Screening
- Neonatal period

Newborn Screening (NBS) Criteria

- Initial Wilson and Junger criteria 1968
  - Important health problems with latent or early asymptomatic stage
  - Natural history well understood
  - Screening and confirmatory testing cost effective
  - The test should be acceptable to the population
  - Acceptable treatment intervention and facilities available
  - Agreement on whom to treat as patients
  - The cost of case finding should be balanced in relation to the possible expenditure on medical care as a whole
  - Case finding should be a continuing process.

Wilson and Junger. Public Health Papers 34. World Health Organization: Geneva, 1968

Newborn Screening System



Newborn Screening - History

- 1961 – Guthrie and Phenylketonuria (PKU)
- 1970s – Sickle Cell
- Others: Hypothyroidism, Galactosemia, MSUD, Homocystinuria, CAH, etc
- 2000 – Tandem Mass Spectrometry (MS/MS) allowed for expansion of the diseases screened
- Non blood-based screening was added
  - Newborn Hearing screening (started 1999)
  - Critical Congenital Heart Disease screening (2014)

Texas NBS History

- 1963 – Phenylketonuria (PKU)Pilot
- 1965 – Mandated PKU Screening
- 1978 – Added Galactosemia and Homocystinuria
- 1980 – Added Congenital Hypothyroidism. Recommended a second screen
- 1983 – Stopped Homocystinuria and started Hemoglobinopathy screening. Mandated a second screen
- 1989 – Added Congenital Adrenal Hyperplasia
- 1995 – Added second-tier DNA test of hemoglobinopathies
- 2000 – Added newborn hearing screening
- 2003 – Working group convened to consider expansion of Texas NBS using the new MS/MS technology

Texas NBS History

- 2005 – House Bill 790 mandated expansion to the ACMG-recommended 29 condition panel as funding allowed
- December 2006 – 1st abnormal MS/MS results reported
- January 2007 – Added Biotinidase deficiency
- December 2009 – Added Cystic Fibrosis
- December 2012 – Added SCID
- 2014 – Added Critical Congenital Heart Disease
- 2015 – Added MS/MS secondary targets

With updated technology

- It became possible to screen and diagnostically test conditions falling outside the Wilson and Junger criteria
  - Limited natural history information
  - Follow-up testing may be more invasive or harder to get
  - Good treatments are not available

But is This Genetic Testing?

- Most is looking at a phenotype.
- Some is done secondary to an abnormal biochemical screen
  - Cystic fibrosis mutation panel
  - Common variants for Galactosemia and MCAD
  - Gene sequencing for VLCAD
- Some is direct genetic testing
  - Severe Combined Immune Deficiency (SCID)
    - T-cell receptor excision circle (TREC)
  - Spinal Muscular Atrophy
    - *SMN1* copy number

Genomic Sequencing of Newborns as Diagnostic Testing

- Symptomatic Newborn
- Genomic testing can be useful if
  - Phenotype does not fall into a defined syndrome or syndrome family and cytogenetic testing is not diagnostic
  - Recognizable phenotype but directed gene panel is not diagnostic
  - Lethal condition with limited time to get testing done
- Trio testing – sample from patient and both parents

Genomic Sequencing of Newborns as Screening

- Idealized goal: To identify newborns with genetic conditions that may be prevented, ameliorated, or treated prior to onset of symptoms.
- Pros tend to be practical planning
- Cons tend to be more nebulous

Newborn Screening Criteria

- Wilson and Junger criteria
  - Important health problems with latent or early asymptomatic stage
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Wilson and Junger. Public Health Papers 34. World Health Organization: Geneva, 1968

Important Health Problems

- Current NBS
  - Overall detects abn in ~1/500 NB
  - Any individual condition is less, down to 1/million
  - Some conditions have never been detected in a given state
- WES/WGS
  - More ‘less common’ conditions
  - Conditions with mild phenotypes

Feuchtbaum et al, Genetics in Medicine 2012;14(11):937-945

Latent or Early Asymptomatic Stage

- Current NBS
  - Meets this criteria by definition
- WES/WGS
  - More treatable conditions that are not amenable to biochemical or marker screening
    - Rady Children's Hospital Rapid WGS study
  - How long is "Latent"
  - What is "Asymptomatic"


L.A. NOW LOCAL LA TIMES

Decoding your baby's DNA: It can be done. But should it be?

By SOUMYA KARLAMANGLA APR 22, 2018 | 6:30 AM

Farnaes et al. Genomic Medicine, 2018 Apr 4; 3:10

Testing of Minors

- The American College of Medical Genetics and Genomics (ACMG) and the American Academy of Pediatrics (AAP) recommend against predictive genetic testing of minors when there is no anticipated change in medical management prior to adulthood.

Ross et al, ACMG Policy Statement. Genetics in Medicine , 2013:15(3):234-245.

Natural History Well Understood

- Current NBS
  - Screening ⟷ Management
  - Secretary's Advisory Committee*
  - Already pushes this boundary
- WES/WGS
  - Broader ability to find well-defined conditions and provide specific diagnosis early
  - Variants of Uncertain Significance
  - Genes of Uncertain Significance

https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html

Screening and Confirmatory Testing Cost Effective

- Current NBS
  - $55.24 in Texas (US range $0 - $150)
  - Follow-up testing for positives varies by condition
  - Vast majority covered by insurance
    - “Cost” includes time, travel, day(s) off work
- WES/WGS
  - The first one was ~$2.7 billion and took 13 years
  - Now $1000 - $2000 – varies by lab

Test Acceptable to the Population

- Current NBS
  - Heel stick blood draw
  - Chemistry test
    - In big context, not different from cholesterol or other
- WES/WGS
  - Venipuncture blood draw
  - DNA testing
  - “Genetic mystique”
    - Expecting more than testing will tell
    - Not realizing what it might reveal
  - No such thing as “Whole”

Bancroft, J Adv Nurs 2010;66:710-737; Tassicker et al, Eur J Hum Genet 2009;17:66-70; Creighton S et al, Clin Genet 2003;63:462-475; Meiser and Dunn, J Neurol Neurosurg Psychiatr 2000;69:574-578

Acceptable Treatment Intervention

- Current NBS
  - Defined treatment protocols/Standard-of-Care
  - Not all are simple
- WES/WGS
  - Defined treatment protocols/Standard-of-Care
    - What about late onset conditions?
  - Most will have no treatment
  - Heck, we can't agree about brain MRIs in NF1

Treatment Facilities Available

- Current NBS
  - Defined Specialty Providers throughout Texas
- WES/WGS
  - Existing healthcare system
  - Post-test Genetic evaluation and counseling
  - Variant reclassification
    - Cancer reports
      - Overall 1,673,303 reports: 60,064 (3.5%) amended
      - UTSW 9493 reports: 582 (6.1%) amended

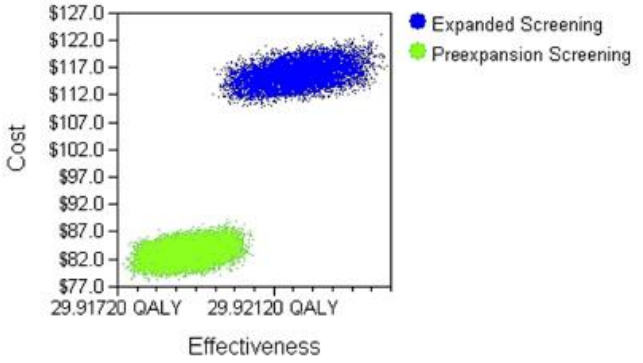
Mersch et al, JAMA, 2018;320(12):1266-1274

Agreement on Who is a Patient

- Current NBS
  - The baby with positive screen/increased risk
- WES/WGS
  - Persons with shared genetics
    - Genetics in the context of the family
  - Will identify carriers (talk about carrier screening in minors)

Cost Balance

- Current NBS
  - Price of testing ($55.24) pays for the testing and follow-up. So that is cost neutral.
  - Cost of testing is balanced by preventing complications.
- WES/WGS
  - Unknown



Tiwana et al, JVAL 2012: 613-621

Ongoing Case Finding

- Current NBS
  - Mandatory samples at 24 hrs and 7-14 days
- WES/WGS
  - Yet to be established

Complexities

- Cost
- Testing lab availability
- Need for adequate post-test (and ideally pre-test) family counseling
- Genotype is not necessarily predictive of disease onset or severity
- There is more unknown than there is known

AND

There is no such thing as “normal” in genetic testing

ACMG

- WGS/WES should not be used at this time as a first-tier approach for newborn screening.

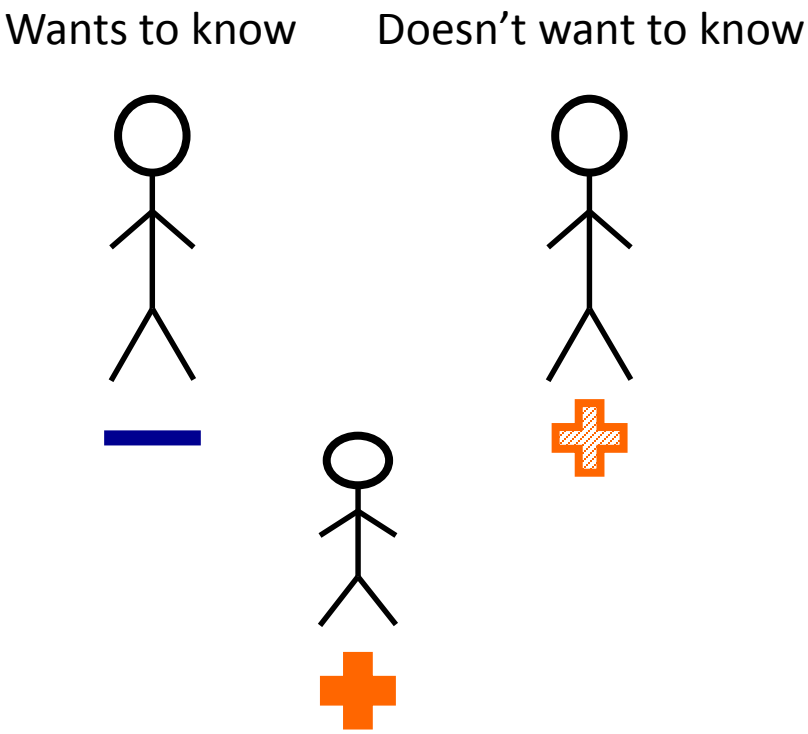
- "Asymptomatic individuals interested in WGS/WES for purposes of health screening should receive both pre-test and post-test counseling from a trained medical geneticist and/or affiliated genetic counselor. They should be informed of the potential risks and benefits of such testing and the virtual certainty of finding variants of uncertain significance. The threshold for determining which results should be returned to individuals seeking screening should be set significantly higher than that set for diagnostic testing due to the much lower *a priori* chance of disease in such individuals."

ACMG Policy Statement: http://www.acmg.net/PDFLibrary/Genomic-Sequencing-Clinical-Application.pdf

Incidental Findings

- Pathogenic or likely pathogenic variants in any of 59 genes
- High penetrant genetic disorders
- Medically actionable
- Opt in/Opt out choice during pretesting informed consent
  - If consent not obtained, lab will withhold results
- Pharmacogenetic risk

ACMG Policy Statement: http://www.acmg.net/PDFLibrary/Reporting-Incidental-Findings.pdf



They both want to know about secondary finding in the child

Hastings Center

- NSIGHT: Newborn Sequencing in Genomic Medicine and Public Health
  - Four sites + NIH
  - Projects to "explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period"
    - Genomic testing in clinical medicine
    - Genomic sequencing at a population level
    - Ethics and Policy Advisory Board

Hastings Center Report, July-August 2018 (whole issue)

Clinical Context

- Targeted testing/WES/WGS is useful in diagnosis of symptomatic newborns with parental permission and access to genetic counseling and follow-up
- Results unrelated to the diagnosis may be returned to the families if the families could benefit
- Targeted testing/WES/WGS should not be used as a screening tool
  - Limited usefulness in asymptomatic populations
  - Concerns regarding storage of results
  - Potential discriminatory or insurance uses
  - Potential to generate unnecessary distress
  - Potential to require health resources for follow-up, monitoring, and counseling.

Johnston et al, Hastings Center Report, July-August 2018:S2-S51

Public Health Context

- WES/WGS should not be used as the sole screen in state-sponsored NBS programs.
- Targeted sequencing may be used
  - As a secondary test after a positive screen
  - As a primary test when sequencing is the more appropriate or only method for screening a particular condition

Johnston et al, Hastings Center Report, July-August 2018:S2-S51

NSIGHT Ethics and Policy Board

"While we recognize the considerable benefit in using targeted sequencing to screen for or detect specific conditions that meet the criteria for inclusion in newborn screening panels, use of genome-wide sequencing as a sole screening tool for newborns is at best premature."

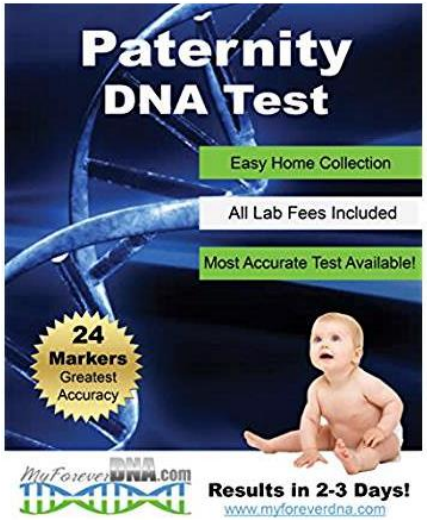
Johnston et al, Hastings Center Report, July-August 2018:S2-S51

Direct-To-Consumer (DTC) Context

- Parents should not use DTC sequencing on their newborn.
- And health care providers should recommend against it.

Johnston et al, Hastings Center Report, July-August 2018:S2-S51

DTC Testing



23andMe

ancestry

Promethease Login

Before you may use Promethease to retrieve information about the human genome, you must read and agree to the following statements. Please read each statement and check the box next to each one and then click 'I Agree'.

- [ ] I understand that the information provided in my Promethease report is based on SNPedia.com and that my report is for educational and research purposes only.
- [ ] I understand that my report is deleted after 45 days but that I can download it before it is deleted and that I can regenerate it, if I create an account.
- [x] I realize that most published reports about DNA variations explain only a small part of the heritability of a trait, and they also don't take into account how different variants might interact. In addition, published reports typically ignore environmental, dietary, microbial, medical history and lifestyle factors, any or all of which may well affect my true risk for any trait or disease.
- [x] I am aware that I am strongly encouraged to discuss my Promethease report with a doctor, genetic counselor or other health-care provider prior to making any medical or reproductive decisions. I also acknowledge that I am advised to confirm any significant finding discovered in part through the use of Promethease by an independent, clinically validated test for use in connection with the medical trait in question.
- [ ] I have read and understand the Privacy Policy and the Legal Terms and Conditions of this website. I agree to these conditions.
- [x] I accept the risk of learning that I may be at high risk for a debilitating disease.

I do not agree | I agree

DTC Testing Points

- Many (most?) DTC tests don't give specific normal/abnormal results. They note increased or decreased risk.
  - Interpretation requires patient-specific information
  - 40% false positive rate
- Privacy concerns including
  - Who will have access to the test results
  - What happens to the DNA sample
  - Whether test results have implications for life, disability or long-term care insurance
  - Whether data generated will be sold to/shared with third parties
  - Who owns the data?

Tandy-Connor et al, Genetics in Medicine, 2018 Mar 22. doi: 10.1038/gim.2018.38
ACMG Policy: http://www.acmg.net/PDFLibrary/Direct-To-Consumer-Genetic-Testing-Policy-Statement.pdf

Summary

- There is no disagreement about using targeted and genomic sequencing as diagnostic testing in symptomatic newborns.
- Advantages of newborn genomic sequencing as screening
  - Single test needed
  - Will find a larger number of potentially treatable conditions
  - May identify conditions for which early management would mitigate risk
  - May assist parents in reproductive decision making
- Disadvantages of newborn genomic sequencing as screening
  - Cost
  - Concerns regarding storage of results.
  - Possibility of identifying late-onset conditions relevant only in adulthood
  - Potential discriminatory or insurance uses
  - Limited usefulness in asymptomatic populations
  - High likelihood of variants of uncertain significance needing health resources for follow-up, monitoring, and counseling, which add a psychological burden

Thank you

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