Genetics and Ethics in the Newborn: The Future is Now H2013: Joint Program: Section on Bioethics and Section on Perinatal Pediatrics

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Disclosures

• In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

1. Review the history of newborn screening [NBS] (metabolic/genetic) of children and its expansion to include the platform technology of tandem mass spectrometry [MS/MS]

2. Examine the benefits and risks of NBS (metabolic/genetic) in the neonatal intensive care unit [NICU] setting

3. Consider the pros and cons of using whole genome sequencing [WGS] in NBS
The History of Newborn Screening

• NBS for phenylketonuria [PKU] began in the early 1960s after Guthrie developed blood test—Bacterial Inhibition Assay—and the filter paper card on which to collect the blood.

• Controversial at the time
  – Government telling doctors how to practice
  – Not clear that we knew who should be identified as affected and how to treat them or for how long.
Ten criteria for population screening

- World Health Organization (WHO) report by Wilson and Jungner in 1968.
  - Although not specifically designed for newborn screening, it was used, with slight modification, for the next 3 decades.
  - These criteria include an adequate understanding of the natural history of the condition, a recognizable latent or early symptomatic stage, and an agreed policy regarding whom to treat as patients.

<table>
<thead>
<tr>
<th>Box 3.1.1 Wilson and Jungner classic screening criteria, WHO 1968</th>
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<td>1. The condition sought should be an important health problem.</td>
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<td>2. There should be an accepted treatment for patients with recognized disease.</td>
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<td>3. Facilities for diagnosis and treatment should be available.</td>
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<td>4. There should be a recognisable latent or early symptomatic stage.</td>
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<td>5. There should be a suitable test or examination.</td>
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<td>6. The test should be acceptable to the population.</td>
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<td>7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
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<td>8. There should be an agreed policy on whom to treat as patients.</td>
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<td>9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.</td>
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<td>10. Case-finding should be a continuing process and not a 'once and for all' project.</td>
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Slightly updated by UK National Screening Committee, “Criteria for appraising the viability, effectiveness and appropriateness of a screening programme”. On the web at: http://www.screening.nhs.uk/criteria
Initial expansion of NBS was slow

- 1963: Guthrie: PKU screening
- 1968: World Health Organization (Wilson and Jungner Principles)
- 1973: Dussault: congenital hypothyroidism screening
- 1973: Garrick hemoglobinopathy screening
  - Not implemented into NBS until 1989
  - (needed to prove it could reduce morbidity or mortality)
- 1977: Pang and Neu: CAH screening
- 1982: Colorado screens for CF using IRT
  - Expansion will not occur until gene identified in 1989
- 1984: Wolf: biotinidase deficiency screening

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Tandem Mass Spectrometry (MS/MS)

• Mass spectrometry developed shortly after WWI.
• The process of tandem mass spectrometry (2 spectrometers in tandem) was developed for use in NBS in the 1990s.
• The development of a platform technology like MS/MS enables us to screen for many conditions simultaneously with one sample.
MS/MS and its adoption into NBS

• The adoption of MS/MS in some states led to wide variability in the number of conditions included in each state’s newborn screening panels.

  – Early 2000s: West Va screened for 4 conditions; Michigan for 40 conditions

  – Today, all screen for the conditions included in the recommended “Uniform Panel” although some states screen for additional conditions
    • New York for Krabbe Disease
    • IL and MO for a number of Lysosomal Storage Disorders
Expansion and Standardization of NBS

• In 2002, the Maternal and Child Health Bureau Health Resources Services Administration (HRSA) commissioned the American College of Medical Genetics (now the American College of Medical Genetics and Genomics or ACMG) to outline a process of standardization of outcomes and guidelines for state newborn screening programs.

• In 2005, the ACMG/HRSA Committee proposed a “uniform panel” including 25 primary and 29 secondary conditions.
  – Strong support from parent advocacy groups
  – Strong criticism from some scientists and ethicists

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Critics of the ACMG Report

• Two-part Methodology. The main component was a survey of all stakeholders for 84 potential conditions to be included in a uniform newborn screening panel
  – Invitation to participate by email to genetics community and parent/patient advocacy groups.
  – 3 of the conditions were infectious diseases (HIV, CMV and Toxo). No email directed to individuals with this expertise
    • (and so the committee just ignored these conditions)
    • No invitation to general pediatricians despite the concept in pediatrics of the Medical Home
• The ACMG survey has no coherent analytic framework.
  – Some questions ask about objective facts such as the incidence of the condition.
  – Other questions mix fact and value. For example, one question asks the respondent to rank the burden of the untreated condition on a 5-point scale (assumptions about the consequences for the infant with his or her normative judgment about how serious a burden those consequences represent.)
  – No justification is provided for the weights assigned to different responses on the survey.
    • For example, 200 points were awarded to a test if it was known to be associated with a life-saving treatment, but a test could also be awarded 200 points if it could be performed on a multiplex machine regardless of whether it had any proven benefits.
  – Weighting was changed after early votes came in (but early scores were not discarded nor were the respondents asked to re-evaluate)
• The second part was a systematic literature review
  – This was never completed
The Fate of the Uniform Panel

• Endorsed by the Secretary’s Advisory Committee on Heritable Disorders of Children and Newborns despite the fact that...
  – ...at the time of endorsement, the report was not finished and therefore not read by the Committee.
  – ...systematic literature reviews for each condition were not done.

• Despite this, Uniform Panel adopted by all US states within a few years.
Problems with the Uniform Panel

• Some “conditions”: no currently available treatments
• Some “conditions” may not be “conditions”
  – 2-methylbutyrl-CoA Dehydrogenase Deficiency (2-MBAD)
    • Before MS/MS only 5 cases identified
    • In first 5.75 years, Wisconsin identified 27 infants, all but one were infants born to Hmong families.
    • Virtually all are asymptomatic despite relative non-compliance with diet.
  – Short-chain acyl-coenzyme A dehydrogenase deficiency and 3-methylcrotonyl-coenzyme A carboxylase deficiency are currently screened disorders for which recent large-scale population-based studies report difficulty in determining who will develop severe vs. asymptomatic disease.
• Although the Secretary’s Advisory Committee (now the Discretionary Advisory Committee) created a new set of criteria to identify appropriate conditions after the dust settled, and claims it will remove conditions that are not appropriate for population screening, no condition has been removed.
NBS in the NICU

Why should the neonatologist care?
Newborn Screening in the NICU

• Low birth weight and preterm infants pose a special problem for NBS programs
  – Many infants require TPN which leads to many false positives
    • A protocol interrupting total parenteral nutrition for 3 h before newborn screening collection resulted in a 74% reduction in false-positive results in a neonatal intensive care unit.
  – Many infants require blood transfusions which interferes with some tests (e.g., hemoglobin electrophoresis)
  – Reference ranges established for healthy full-term infants leading to many false positives (and some false negatives)
NBS in the NICU--many false positives

• The two most common false positives: thyroid disease and congenital adrenal hyperplasia
• Congenital adrenal hyperplasia (CAH)
  – Need to correct for gestational age and birthweight
  – Best for salt-wasting; less accurate for more mild disease in preterm infants.
• Several patterns of thyroid dysfunction in preterm infants
  – Most common pattern is transient hypothyroxinemia of prematurity (THOP)
    • Controversial whether treatment is beneficial and possible increase risk of circulatory collapse and NEC
  – Primary hypothyroidism (low T4 with elevated TSH).
    • (although they may have a delayed TSH so repeat testing is important)
      – Although again most of these cases are transient
  – Nonthyroidal illness (NTI)
    • Serum T3 inversely related to markers of systemic inflammation
The Next Frontier: Expanding NBS Using Whole Genome Sequencing (WGS)

First sequence took over a decade and cost over 3 billion dollars
Now sequencing can be done in days and costs as little as $1000
The $1k genome, the $100k analysis
ER Mardis. Genome Medicine 2010; 2: 84

• The required expertise to “solve” each case included molecular and computational biologists, geneticists, pathologists and physicians with exquisite knowledge of the disease and of treatment modalities, research nurses, genetic counselors, and IT and systems support specialists, among others.

• ...one does wonder how, in the clinical translation required for this practice to become commonplace, such a “dream team” of specialists would be assembled for each case.

• In other words, even if the cost and speed of generating sequencing data continue their precipitous decreases, the cost of “team” analysis seems unlikely to immediately follow suit.
WGS in NBS

• 2010: NICHD sponsored a symposium to develop a research agenda around the “application of new genomics concepts and technologies to newborn screening and child health”

• 2012: NIH put out an RFA for proposals to assess the potential value and challenges of integrating genomic sequencing into NBS programs
  – 4 funded for $25 million over 5 years

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DETOUR: The Politics and Policies regarding WGS in children?

...and their implications for newborns
Disclosures

• I was a member of the American Academy of Pediatrics (AAP) Committee on Bioethics (COB) and a member of the American College of Medical Genetics and Genomics (ACMG) Social, Ethics, and Legal Issues (SELI) committee when the 2 committees worked together to write a policy statement and technical report entitled Genetic Testing of Children.

• Writing policy involves compromises. While the committee members came to consensus, not every member of each organization agrees with all of the recommendations.
The AAP and ACMG agreed to co-write a new statement on the Genetic Testing of Children in 2009 (although it would not be finalized until 2013)

• Earlier statement by AAP written by its Committee on Bioethics in 2001.
• Earlier statement by ACMG written with the American Society of Human Genetics (ASHG) in 1995.
  – In 2009, ASHG stated it was no longer writing policy statements
  – (In 2015 ASHG published a statement on Genetic Testing of Children)

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AAP/ACMG statement underlying moral principle

- Consensus that moral justification was “the best interest of the child”
- In the pediatric bioethics literature, there is no consensus on what “best interest” means, what interests should be included, whether to include only self-regarding or to also include other-regarding interests, how to balance short-term and long-term interests, and whether to include child’s autonomy as a component of best interest (UK versus US)
- (ASHG statement also based on best interest)
Time-Line of Guidance on WGS

• February 2013: AAP/ACMG statement on Genetic Testing of Children was published on-line
  – ACMG had asked to exclude discussion of WGS because 1) it was still research; and 2) they were writing a more comprehensive statement.
  – Joint statement reads: Genetic research (including the use and retention of dried blood spots and whole-genome sequencing) is beyond the scope of this technical report and accompanying policy statement.

• March 2013: “ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing”
  – By “incidental findings” they meant findings that are beyond those needed to answer the clinical question for which sequencing was sought.

• Gist of the new policy: if sequencing is performed for any clinical purpose in children or adults, a specified list of 56 genes associated with 24 inherited conditions should be assessed, in addition to the genomic information for which testing was sought.
  – Supporters call this “opportunistic screening”; critics call it a “mandatory hunt”
  – Regardless, neither patient nor ordering physician consent is needed.
Ethical issues raised by the “List of 56”

- Does not require consent of ordering physician
- Does not require consent of patient
- Why secondary findings in WGS is different than “secondary or incidental findings in Radiology
  - To identify these “secondary findings”, you must interrogate the specific genetic areas and then interpret the findings (which may require some study of the current literature).
    - (In contrast, the mass in the kidney is seen when you x-ray the abdomen for liver concerns)
    - Not clear who is paying for this additional work
- The genes are highly penetrant in high-risk communities, whether they are highly penetrant in low-risk communities is not known
  - E.g. BRCA
    - Andreasen et al. found that some of the cardiac genes included in the ACMG mandatory hunt are less penetrant than previously thought. (*Eur J Hum Genet* 2013; 21: 918-928)
ACMG clarification (April 2013)

• Large amount of push-back from many stakeholders
• In response, ACMG published a clarification in which they reaffirmed that testing should be based on “best interest of the child”
  • Affirms its recommendation not to perform diagnostic testing for an adult-onset condition in children, but believes that reporting severe, actionable, pathogenic mutations fall outside this recommendation.
• Example: Disclose incidental BRCA-1 finding because:
  – 1) If the child carries a pathogenic mutation there is a high probability that one parent does as well.
    • the child benefits by potentially preventing a severe adverse health outcome in a parent.
ACMG clarification (April 2013, cont.)

• Denies that it is inconsistent with AAP/ACMG report
  – The AAP/ACMG recommendation: Do NOT test children for an adult-onset disorder in high risk families—because in those families it is expected that the child will be offered testing at an age when he or she can make an informed decision about testing.
    • Here family has no reason to suspect risk status
    • Of course, we don’t have data that these variants are highly penetrant in these communities
ACMG clarification (April 2013, cont.)

• ACMG concedes that patients and physicians should have the right to refuse mandatory hunts.
  – Permits opt-out
• ACMG still assumes that parents should get predictive information about their child’s risks (which may inform them about their own risks).
  – Despite the clarification, it contradicts the joint statement.

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What’s the problem with “opportunistic screening (aka, a mandatory hunt) in children?

• There is consensus against predictive genetic testing of children for adult-onset conditions
  – Most of the genes included in the mandatory hunt are conditions that present in adulthood

• In pediatrics (and probably in adult medicine as well), mandatory hunts for high risk alleles in the low-risk population is still experimental and should ONLY be done under a research protocol with IRB approval.
Even without requiring a mandatory hunt, “incidental findings” are a significant issue in WGS? (as is the identification of variants of unknown significance [VUS])
WGS and Incidental Findings

- Kohane IS, Hsing M, Kong SW. Taxonomizing, sizing, and overcoming the incidentalome. Genetics in Medicine 2012; 14(4); 399-404.

- Incidental Finding: “findings that have potential health or reproductive importance and are discovered in the course of conducting research but are beyond the aim of the study”
  - False positive: provide misleading and/or incorrect diagnostic or prognostic information

- Study involved 9 “healthy” individuals
Why is this important for neonatologists (and other pediatricians who care for infants)?

Whole Genome Sequencing in the nursery

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Using WGS for diagnostic purposes in children

• WGS as part of the diagnostic work-up of an ill child is expanding.
  – In 2011, first case where sequencing led to a treatment that saved a child’s life
Using WGS for NBS

• Bhattacherjee and colleagues developed a targeted next-generation sequencing panel coupled with a variant processing pipeline that focuses directly on 126 genes related to newborn screening diseases and is applied to the exome or a next generation sequencing panel.
  – Our ability to pinpoint the clinical phenotype of an individual on the basis of “genotype” alone is still in its infancy; in our case, only 27 of 36 NBS disease cases were classified correctly without phenotype information.
  – It is typically assumed that, at least for monogenic disorders, the genotype–phenotype relationship would be simple.
  – With the clinical phenotype description, single-nucleotide variations in exons, introns (up to 30 bp away from an exon), and indels were correctly detected in 32 of 34 Amish or Mennonite disease cases and two carrier cases.
    • (Phenotypic details usually won’t exist for newborns...)


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WGS in the nursery

• WGS has the potential to aid in diagnostic dilemmas.
  – Targeted selection of genes
  – Often used after more narrow genetic tests have failed to make a diagnosis

• Can WGS replace MS/MS
  – Will not identify hypothyroidism
  – Study by Bhattacherjee and colleagues shows that it is not ready for prime-time:
    • Lot of genotypes that do not correlate with phenotype

• Problems with using WGS in NBS
  – Increase in false positives; indeterminate results, overdiagnosis; and carriers
  – Issues of consent, storage of data, parental and physician education, and genetic counselling services
Attitudes about WGS in NBS

• GENETIC PROFESSIONALS:
  – 85% of genetic professionals felt that WGS should not be currently used in NBS, and that if it were used, 86.5% felt that it should not be mandatory.
    • 75.7% foresee it as a future use of WGS
    • Ulm et al. “Genetic Professionals’ Opinions of Whole-Genome Sequencing in the Newborn Period.” J Genetic Counselling 2015; 24: 452-463

• PUBLIC:
  – (online surveys; individuals sign up and get incentives for completing surveys)
  – Over 2/3 of US parents were “very interested” or “somewhat interested” in WGS for newborns
    • Goldenberg et al. “Parents’ interest in whole-genome sequencing of newborns.” Genetics in Medicine 2014; 16: 78-84
  – Canadian residents would be LESS willing to participate in NBS if it used untargeted genome sequencing methodologies (80% vs. 94%)

• Remember: public advocacy groups have been very instrumental in the adoption of PKU screening in the 1960s and in the expansion of NBS to include MS/MS in the 1990s and 2000s.

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Pushback against the use of WGS in NBS

1) Statement written by the Public and Professional Policy Committee of the European Society of Human Genetics, the Human Genome Organisation Committee on Ethics, Law and Society, the PHG Foundation and the P3G International Paediatric Platform, January 2015 (Ellen Clayton, a former member of the AAP Committee on Bioethics participated in the writing of the statement).

2) The ASHG statement on the genetic testing of children, July 2015 (the lead author was Jeff Botkin, a former chair of the AAP Committee on Bioethics).
European statement regarding the use of WGS in NBS

- Focus on the best interest of the child.
- It still has to be proven whether the implementation of new sequencing technologies and approaches in NBS would be an effective public health strategy.
- The responsible use of genome sequencing within a public health programme such as NBS should not be technology driven, but rather be adopted on the basis of its public health potential. The primary justification for performing genome sequencing within the context of NBS should be the health interests of the child.
- At this time, we recommend a targeted sequencing or targeted analysis approach.
The 2015 ASHG recommendations on Genetic Testing of Children addressed WGS:

• Supports basing decisions on best interest, but concedes that “defining an individual child’s “best interest” is often complex and controversial…”

• With respect to newborn screening, argues that “state programs only introduce new conditions on a mandated NBS panel after a thorough review of the evidence…”

• Recommends using least comprehensive genetic test necessary

• Regarding whole genome sequencing: genome scale sequencing is not indicated for the purposes of clinical newborn screening at this time
Concluding Thoughts: Genetics and Ethics in the Nursery

• The role of genetics for diagnostic purposes is expanding in all age groups
  – Unfortunately, treatments lags behind
• Population screening of newborns (NBS) remains one of the most successful public health measures. Conditions tested should meet the Wilson and Jungner criteria (with modifications)
  – The Secretary Advisory Committee’s has evaluated a number of conditions using its newer methodology.
    • It has rejected Krabbe disease (although Krabbe disease is being tested for in a number of states due to parent advocacy groups)
    • It has approved SCID (severe combined immunodeficiency disease)
  – Some argue that some of the Wilson and Jungner criteria become less important as platform technologies that allow screening for many conditions at once.
    • This objection may deny the costs of “newborn screening as a system”
• WGS in the nursery will only compound the problem of expanding beyond Wilson and Jungner.
  – If used in the nursery, the focus should be on identifying conditions that present in infancy for which treatment can modify the course of the disease.
  – The mandatory hunt for secondary findings should be avoided.
Changes you may wish to make in your practice:

• Counsel parents about the benefits and risks of newborn screening; Encourage screening for the conditions in the uniform panel.

• Become familiar with problems of screening of premature and ill infants; ensure appropriate follow-up for screen positives.

• Become familiar with your own state’s screening panel (does it conform or go beyond the uniform panel?)
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• Mardis ER. The $1,000 genome, the $100,000 analysis? *Genome Med* 2010; 2(11): 84.

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