Possible Futures for Newborn Screening

Genomics in NBS: scaling up

50 Years of Victorian Newborn Screening: Past, Present and Future
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Russell J Howard
Head, Commercial Strategy,
Kinghorn Centre for Clinical Genomics
Garvan Institute of Medical Research
Sydney
Our genome: the basics

- we have 37 trillion cells in our body
- each cell contains 2 genomes of 3.2 billion DNA letters
- the DNA code is a 4 letter language (ATGC)
- our genetic material is arranged in 23 pairs of chromosomes
- there are ~ 20,000 protein coding genes and ~250,000 proteins (different gene arrangements) = 1.5% of the genome
- 98.5% of genome is in between these genes: gene regulation, control at various levels. Genetic changes in these regions can cause clinical disease
- we are 99.9% identical
- we are all different by about 3 million variant positions from the next person
Mendelian disorders: the Medical Problem

- rare monogenic diseases: single locus, “monogenic”
- 8,000 named Mendelian Diseases identified
- >3,500 of known molecular basis
- 4% of births, not rare collectively
- leading cause of infant death, ~25% of deaths, ~15% of pediatric hospital admissions, impact 4X higher in some consanguineous populations
- @ 320,000 births/year in Australia, >6,000 children/year

Mendelian Disease Genes Published per Quarter

Mendelian gene discovery:
Accelerating to ~20 new Mendelian disease genes/month
The primary allele for most Mendelian disorders will be identified in 5 years
The Diagnostic Odyssey

Clinical Problem

Try Again

Differential Diagnosis

Interpretation

Genetic Testing (1-N genes)
Screening ill babies with suspected genetic disease

- 20-40 conditions are identified via classical heel prick screen: classical NBS

- Screening sequentially with individual molecular tests (a “gene screen”) for one or more disease genes ($80-$2,000 per test: $2,000-$30,000 in total costs)

- Screening with panels of 20-200 genes ($1,000-$2,000)

- Screen all protein coding genes (~20,000) using whole exome sequencing (WES: SA Pathology, Genetics & Molecular Pathology, NATA accredited)

- Screen the entire genome, coding and non-coding sequence, using whole genome sequencing (WGS: coming soon in Australia)

*Obtain the right genetic information, fast, at the right price, with acceptable false positive and false negative rates, and handle the information appropriately and ethically for benefit of child and parents*
Arrival of the “$US 1,000 genome”

One whole genome sequence (WGS) costs ~US$1,000 before bioinformatics, variant analysis and contributions of clinical geneticist/pathologist.
Whole Genome Sequencing: basics

**Child’s Genome**

180,000,000,000 DNA letters detected in Genome fragments
3,000,000,000 DNA letters assigned to the sick child
("genome sequence")
4,800,000 DNA letter changes different to “normal”
1,000,000 DNA changes in <1 in 100 people

**Child’s symptoms**

Interrogate database linking changes in DNA to clinical phenotype
Computer generated list of potential diagnoses ~1,000
Identify 1-2 DNA changes in **this child** that could relate to symptoms
Diagnosis: to be confirmed

- WGS is less expensive per gene/per length of DNA than alternative sequencing methods, but more expensive *in toto*
- only WGS captures variants between the genes for proteins: these variants can also determine health and disease
- WGS allows later reinterpretation *in silico*: when diagnosis fails, research with other children may later provide a clinical diagnosis
Example: WGS of acutely ill newborns

Stephen F. Kingsmore, Rady Pediatric Genomic & Systems Medicine Institute, San Diego; previous, Children’s Mercy Hospital, Missouri, Kansas

- Tested >2,000 children with ultra-rare genetic disease for rapid, early molecular diagnoses and genome-informed treatments

- Randomized, controlled, prospective trial of clinical utility of WGS for rapid diagnosis of severe disease in acutely ill babies with presumed genetic disease

- 26 hours turnaround for WGS and return of diagnosis: case-by-case intense focus to screen for all 8,000 known Mendelian diseases

- Within 1.5 days: stop non-specific treatments, start specific treatments, in one example, liver failure corrected in 1 wk., child now 3 years old, 72 QALYs saved

- With 35 infants screened by WGS, 57% diagnosis rate, 65% of diagnoses had acute clinical utility, strongly favorable impact on outcome in 20% of diagnoses

“A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases”
WGS at the Kinghorn Centre for Clinical Genomics

- KCCG established at Garvan Institute of Medical Research October 2012
- Led by Marcel Dinger
- Multidisciplinary team of 40: laboratory scientists, bioinformaticians, software developers, geneticists and PhD students
- Dedicated to translation of genomic information from WGS to clinical benefit
- A commercial service for NATA-accredited pathology reports based on WGS will be available soon in Australia
DNA sequencing & analysis at Kinghorn Centre for Clinical Genomics

- one of world’s first sites to purchase Illumina HiSeq X10 system: 10 instruments in operation
- full capacity 350 genomes/week [18,000/yr]
- providing research services globally
- NATA accreditation (ISO15189 medical testing) Q1, 2016
Envision a WGS-based NBS for all children

Benefits for the Child

- for ill children best chance of early treatment: WGS provides maximum chance of finding variants linked to a known clinical condition or potential clinical variants (for later elucidation via research)

- for asymptomatic babies at birth, potential early diagnosis and intervention to reduce morbidity & mortality (all well babies are potentially asymptomatic?)

- broad screening results inform natural history of disease and variant forms, eventually yielding improved treatment for the child and others

- if the well child becomes seriously ill at any age, any genetic basis for disease is readily determined from their stored WGS and used to guide diagnosis and treatment: a test at birth for this reason alone is not of immediate clinical benefit to the infant
Envision a WGS-based NBS for all children
Benefits for parents, society, taxpayers

- avoidance of “Diagnostic Odyssey” reduces net cost of treatment

- reducing morbidity and mortality enhances the life of child and family with diverse positive flow-on effects to society

- benefit to families through knowledge may facilitate parental choices around conception, family planning, early focused diagnostics

- expansion of conditions that could be targeted: uncommon conditions (ACMG list, 57 genes & 24 conditions), carrier states, cancer syndromes, variants associated with common conditions (CVD, diabetes, mental health)

- a National database (anonymized) of immense value for clinical research and epidemiology at the national level: better diagnostics and treatments

- a National database (anonymized) for enhanced planning for health policy and planning, staffing, training, budgets

- technically feasible: implementation cost required in many dimensions
Economic Considerations for National NBS program using WGS

- Cost will likely continue to decline: National Program cost < than today’s cost

- Positive predictive value of current tests = 1% - 40%. Published studies show 40-60% predictive value for WGS with some populations of ill children

- Clinical & economic studies required locally to show how rapid WGS-assisted screening adds medical value to child, saves $$, value to parents, hospital infrastructure and services etc.

- Other investments required to set up and manage an on-going program (compute & staff infrastructure, QA/QC, database curation)

- Other National Programs required to integrate and capture full value (Medical Records, uniform clinical reporting standards)

- A National program likely paid by State/Federal Government (insurance contribution?)

- WGS of newborns introduced in context of multiple value points for WGS during lifetime
  # Pre-conception screen of parents
  # Prenatal diagnosis
  # Newborn screening
  # Pre-symptomatic screening of families and individuals at risk
  # Pre-dispositional testing of well adults
  # Disease diagnosis in children and adults

The value of a National NBS program using WGS will be broad in clinical and societal impact
Feasibility of a National NBS program using WGS

>320,000 births /year in Australia, so >320,000 WGS screening tests

this can be done technically (hard work, but not blue-sky)

- we can develop methods to extract enough high quality DNA from a portion of a dried heel-prick blood spot
- 20 Illumina X10 systems can handle >300,000 WGS/year at one or more national centers (and capacity of each machine is steadily increasing)
- computing power can be amassed to handle the load
- cost will decline to total cost/WGS & analysis <$2,000

financial cost in range ~$500-750MM/year: needs justification medically and financially, but not an impossible number

Issue: with current protocols, there are too few clinical geneticists, genetic analysts, pathologists to deliver the same service to all parents as we plan to provide to acutely ill newborns with suspected Mendelian disease. Solution: provide very focused analysis
“BabySeq”: Exemplar of a Clinical Trial to test role of WGS in NBS

- “BabySeq” Project: Genome Sequencing for Childhood risk and Newborn Illness
- Collaboration between Boston Children’s Hospital, Brigham & Women’s Hospital, Harvard Medical School, Baylor College of Medicine

1. 1st randomized trial to explore benefits and risks of genome sequencing on healthy and sick newborns

2. 240 healthy newborns + 240 NICU newborns

- NIH funded, 2013-2018

- WGS & screen 1,700 genes

- all gene variants associated with childhood-onset conditions

- parents and newborns
Challenges for National WGS-based NBS Program

- increasing false positive results:
  - burden of cost and time for secondary tests, emotional burden on family, loss of trust

- risks of over-diagnosis when natural history of condition poorly understood
  (gene variant effects are different in context of other individual-specific changes)

- substantial number of variants of unknown clinical importance: burden to parents and care providers if disclosed, burden to laboratory and clinicians to ascertain clinical validity

- parental anxiety: more information, more concern; residual anxiety after resolution of a false positive result

- incidental findings: ~1% of WGS will have positive findings in relation to the Am. College of Medical Genetic & Genomics list of 57 genes/24 conditions for which there is definite diagnosis and treatment (e.g. breast or colon cancer, cardiac arrhythmia, intellectual disability)

- how to handle adult onset conditions in the child? Traditional emphasis on immediate benefits to child. Issues of future autonomy of child and impact on child and family.

- autosomal dominant findings in child may be of relevance to parents (BRCA mutation)

- ONE SOLUTION: a screen is defined by what you screen and report, not the technology and potential to tell anything else if queried---only screen for what is of value to the child as infant
Age-based metric for decision making on NBS tests

Jonathan S. Berg, MD, PhD, University of North Carolina, Chapel Hill, NC, USA

- plot time window of incidence vs age
Age-based metric for decision making on NBS tests

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- plot time window of incidence vs age
- identify actionable subset suitable for next generation sequencing and NBS
- appropriate consent
- identify non-medically actionable
- consent required for disclosure
- utility for family planning
- some of these conditions will move into NGS-NBS group over time
Age-based metric for decision making on NBS tests

- disclosure (with consent) dependent on age of onset and treatment
- surveillance, early treatment, other actions for child or parents
- not valuable to baby at birth
- some may move into NBS over time as we learn disease mechanism and treatments

- don’t disclose adult onset, non-medically actionable conditions

Jonathan S. Berg, MD, PhD, University of North Carolina, Chapel Hill, NC, USA
Implementation of a National WGS program for Primary Screening of Newborns

- fundamental change in philosophy of newborn screening programs may not be necessary
- large cost increase in NBS (but maybe justified vs $\Sigma$ cost of status quo)
- increase in burden of false & ambiguous information to parents and clinicians
- uncertain benefits TODAY, without local evidence base and robust system to conduct research and longer-term follow-up

BUILD THE FUTURE: potential for great value to ill and asymptomatic newborns and well babies and children-----”THE GENOME GENERATION”

PLAN TO PLAY A LEADERSHIP ROLE IN NBS GLOBALLY
  - Australia has tremendous relevant assets to enhance neonatal clinical care
  - essential to link with clinical research and screening data Nationally
  - National approach critical: provide scale & National QA/QC
  - leverage overseas experience, knowledge and data
  - lead definition of “what we screen” and “what we don’t screen”
Potential Stepwise Build to a National WGS-based NBS Program

1. Solve issues proactively: clinical benefit, social benefit, ethics, public involvement, cost-benefit, implementation plan, legal

2. Clinical Trial across Australia
   WGS Screen or alternative tests,
   Well & ill newborns (refer “BabySeq”, USA)

3. National, WGS-based,
   Commercial Service,
   WGS Screen for ill children & adults
   with suspected genetic disease

4. National, WGS-based,
   WGS Screen for ill newborns
   with suspected genetic disease

5. National, WGS-based,
   Clinical Trial across Australia
   WGS Screen or alternative tests,
   Well & ill newborns (refer “BabySeq”, USA)

6. National WGS-based NBS Program
Acknowledgements