PGT with whole genome sequencing for all patients?

Against

Tony Gordon, CooperGenomics

COGEN 2019

CooperSurgical®
Fertility and Genomic Solutions

Disclosure information:

- *I am a paid employee of CooperSurgical*

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PGT-M with whole genome sequencing for all patients?

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PGT with whole genome sequencing for all patients
Against

- Technical limitations?

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- Technical limitations?

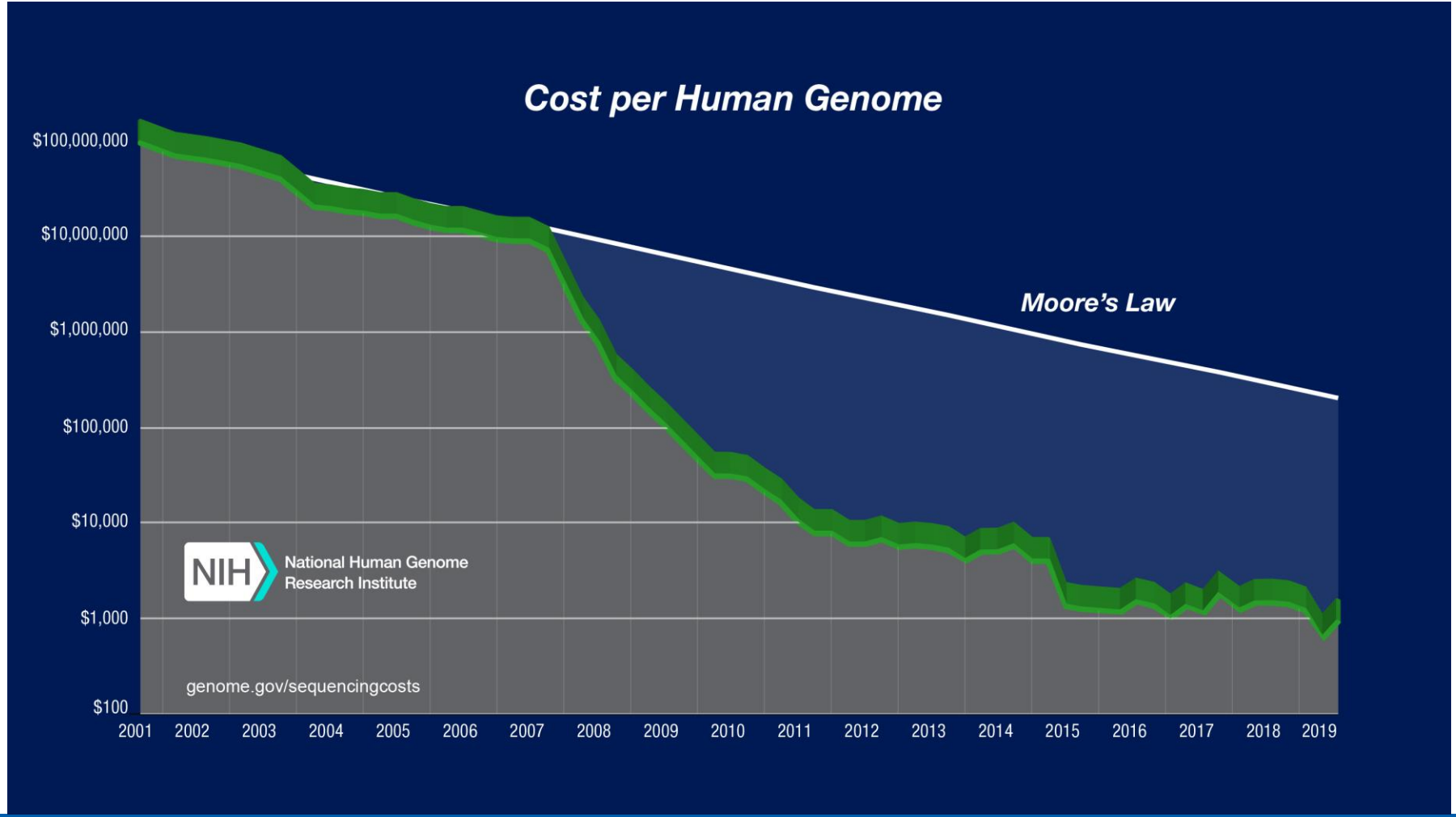
- Clinical / Ethical limitations?

PGT with whole genome sequencing for all patients
Against

- Technical limitations?
- Clinical / Ethical limitations?
- Clinically applicable alternatives to WGS for PGT

PGT with whole genome sequencing for all patients
Against

- Technical limitations?


Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
2001
2002
2003
2004
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2015
2016
2017
2018
2019
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts


News
OMICs
Sequencing
Whole-Genome Analysis
Whole-Genome Sequencing Now Possible for IVF
February 12, 2015
0

PGT with whole genome sequencing for all patients
Against

- WGS Technical limitations?
  - Sequencing highly accurate but there are 3 billion bases in human genome, high level coverage needed
  - x30 coverage needed for variant analysis
  - But “$1000” genome now available?

PGT with whole genome sequencing for all patients
Against

- **PGT** Technical limitations before WGS?
  - Whole genome amplification needed for 5-10 cell TE biopsy
  - WGA - Incomplete coverage for WGS
  - WGA – bias for WGS
  - Allelic drop out / Allelic drop in – not all amplification methods proof read
  - “Low pass PGT-A” x0.6 coverage for PGTai 2.0 suitable for PGT-A/PGT-SR

PGT with whole genome sequencing for all patients
Against

- PGT Technical limitations before WGS?
  - WGS for 4-5 embryos per cycle + maternal/paternal samples
  - Cost?
  - $20K-30K per cycle?

PGT with whole genome sequencing for all patients
Against

- Clinical applications?
  - WGS not ideal for diagnosis of all genetic diseases i.e. triplet expansion disorders, gene/pseudogene disorders
  - Trios of maternal / paternal / embryo biopsy needed for WGS for PGT
  - Even with trios - variant calling still often unclear “unknown significance”
  - Genotype correlations to pathogenicity often unknown

PGT with whole genome sequencing for all patients
Against

- Clinical applications?
- 1:100 births affected by genetic or chromosomal disorders
  - 100’s de novo mutations per embryo
  - Very difficult to confirm de novo mutations by WGS – Sanger sequencing?

PGT with whole genome sequencing for all patients
Against

- Clinical applications?
  - Estimated 4000 single gene disorders - OMIM
  - Genotype – phenotype unclear in majority of disorders.
  - Even common disorders have complex genetics that is difficult to diagnose genotype – phenotype.
  - Variant curation?
  - CooperGenomics provided PGT-M for ~1000 disorders

PGT with whole genome sequencing for all patients
Against

- Ethical?
  - Many single gene disorders have mild symptoms / low cost treatments
  - Countries that license disorders / individual cases consider impact of condition and application for PGT-M. Not possible for WGS?
  - How will you counsel patients where every embryo has 100's pathogenic variants/VUS's, potential disorders, extremely complex report?

PGT with whole genome sequencing for all patients
Against

- Clinically applicable alternatives to WGS for PGT
- 1. Exome sequencing
  - Exome 1-2% of genome
  - x100 coverage possible, technically challenging with WGA DNA
  - Diagnosed majority of genetic disorders
  - Has to be done with PGT-A to confirm euploid embryos?
  - Still costly, huge data interpretation, counselling, ethical challenges

PGT with whole genome sequencing for all patients
Against

- Clinically applicable alternatives to WGS for PGT
- 1. Carrier Screening of parents and classic PGT-M haplotyping to identify unaffected embryos
  - Cost effective (US Healthcare system carrier screening)
  - Directed to actionable disorders (30 – 600 single gene disorders)
  - Reliable technology, well understood for PGT
  - Widely used

PGT with whole genome sequencing for all patients
Against

- Clinically applicable alternatives to WGS for PGT
- 1. Carrier Screening of parents and classic PGT-M haplotyping to identify unaffected embryos
  - Only ~1-2% of couples co-carriers
  - PGT-M directed to co-carriers
  - Limited chance of incidental findings

PGT with whole genome sequencing for all patients
Against

- WGS for PGT – costly, complex
- WGS for PGT – technically difficult to implement due to WGA
- WGS for PGT – clinically difficult to implement, limited additional benefit over other methods
- WGS for PGT – better alternatives in current use

PGT with whole genome sequencing for all patients
Against

- But…….
  - We will use WGS for all embryos at some point in the future

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